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Association between medications and urinary PH

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DOCTORAL THESIS

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Association between Medications and Urinary pH

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I want to thank…

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A mis padres,

mi ejemplo a seguir

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SUMMARY

Background. There are many common disorders/diseases that lead to changes in acid base balance, such as asthma, chronic obstructive pulmonary disease (bronchitis or emphysema), diabetic ketoacidosis, renal disease or failure, any type of shock (sepsis, anaphylaxis, neurogenic, cardiogenic, hypovolemia), stress or anxiety which can lead to hyperventilation, and some drugs (sedatives, opoids) leading to reduced ventilation.

Several factors can influence on urine pH: diet, body surface area, acute water load and exercise. A chronic acidic load can cause a number of health conditions such as osteoporosis, kidney disease, and muscle wasting. Acidic urine pH has been suggested to play an important role in human bladder carcinogenesis by influencing the urine concentration of active aromatic amines. Urine pH also plays an important role in the formation of most types of kidney stones.

Some medications may also influence on urine pH in either direction. However, to date there are no studies that have evaluated the association between medication use and urine pH.

Considering these premises, the present thesis focused on the association between medication use after hospital discharge in a population from the control group of a case – control study of bladder cancer and having constantly acidic urine pH.

Methods. Data collection for this research has been taken from a case-control study on bladder cancer. We have limited subject inclusion and statistical analyses for this report to the control subjects of the case-control study. In the case-control study, 1219 incident transitional cell carcinoma (TCC) cases (84% of 1453 contacted cases) and 1271 hospital controls (88% of 1442 controls) were recruited between June 1998 and June 2001 in 18 hospitals in the following regions in Spain: Barcelona, Vallès/Bages, Asturias, Alicante, and Tenerife. Subjects were 21 to 80 years old at the time of diagnosis and resided in the catchment areas of the 18 participating hospitals. Out of the 611 control subjects with

available valid pH measurements, 598 (97.87%) subjects reported information on vitamins and medications use, and after excluding two subjects with low quality of the interview, and 175 subjects with missing information in the potential cofounders (vegetable intake (n=18), fruit intake (n=15), meat intake (n=89), height (n=85), and weight (n=70), (one subject can have missing information in more than one variable)) we ended with 423 subjects, which is the base population used for this report.

Study participants were trained to test their urine pH with dipsticks twice a day at home (first void in the morning and early in the evening) during 4 consecutive days two weeks after hospital discharge, recording results into a diary together with all medications taken during each of the four days of pH measurements.

To estimate the effects of medication on urinary pH, we calculated odds ratios (OR) and 95% confidence intervals (95% CI) using unconditional logistic regression, with two strategies: a) Fixed terms entered for all potential confounding variables (i.e., age at interview, sex, study region, vegetable intake, fruit intake, meat intake, height, weight, and vitamin C use) plus the medication of interest, building one model for each medication at the segregation levels of 1, 3, 4, 5, and 7 digits of the ATC classification; and b) fixed terms strategy (for all potential confounding factors) combined with step wise strategy entering all medications from a given segregation level of the ATC Classification.

Results. We found statistically significant associations between some medications used by our study population and their influence on urine pH levels: “cardiac glycosides” (OR=7.533, 95%CI: 1.63 – 34.71), drugs acting on “respiratory system” (OR=0.23, 95%CI: 0.07 – 0.81) and “psycholeptics” (OR=0.35, 95%CI: 0.12 – 0.96), that mostly included “anxiolytics” (OR=0.164, 95%CI: 0.041 – 0.647).

Conclusions. Plausible mechanisms discussed, to explain the association between cardiac glycosides with having constantly acidic urine pH could include: the effect of the underlying cardiac diseases for which these drugs are prescribed for, and the direct effect

from such drugs on urine pH.

The association between anxiolytics with not having constantly acidic urine pH would most likely represents the effect of the hyperventilation generated from the underline anxiety disorder for which these drugs are prescribed, rather than a direct effect from such drugs on urine pH.

The association between drugs used in the respiratory system and not having constantly acidic urine pH could be explained by some states of chronic airway diseases, and by the direct effect from these drugs on urine pH.

KEYWORDS**:** Control subjects, urine pH, bladder carcinogenesis, kidney stones, medications, odds ratios, constantly acidic urine pH

RESUMEN

Antecedentes. Muchos trastornos/enfermedades comunes conducen a cambios en el equilibrio ácido-base, tales como el asma, la enfermedad pulmonar obstructiva crónica (enfisema o bronquitis), cetoacidosis diabética, enfermedad o insuficiencia renal o, cualquier tipo de “shock” (sépsico, anafiláctico, neurogénico, cardiogénico, hipovolémico), el estrés o la ansiedad que pueden conducir a la hiperventilación, y algunos fármacos (sedantes, opiodes) que conducen a la ventilación reducida.

Hay varios factores que pueden influir en el pH de la orina: la dieta, la superficie corporal, la carga total de agua y/o la actividad física. Una situación de acidez crónica puede causar distintos problemas en la salud de los individuos, tales como la osteoporosis, la enfermedad renal y/o la pérdida de masa muscular. A su vez, un pH ácido de la orina se ha sugerido que desempeña un papel importante en el desarrollo del cáncer de vejiga humano, ya que influye en el aumento de la concentración de aminas aromáticas activas en la orina. El pH de la orina también juega un papel importante en el desarrollo y formación de la mayoría de las piedras del riñón.

Algunos medicamentos podrían influir en el valor del pH de la orina en cualquier dirección. Sin embargo, hasta la fecha no hay estudios que hayan evaluado la asociación entre el uso de medicamentos y pH de la orina.

Teniendo en cuenta estas premisas, la presente tesis se centra en estudiar la asociación entre el uso de fármacos, en individuos del grupo control en un estudio epidemiológico caso-control sobre cáncer de vejiga tras el alta hospitalaria, y el desarrollo de orina con pH constantemente ácido.

Métodos. La recopilación de datos para este estudio se ha tomado de un estudio caso-control de cáncer de vejiga. Hemos limitado la inclusión de sujetos, para el análisis estadístico de este informe, a la población control de dicho estudio caso-control. En el

estudio caso-control se reclutaron 1219 (TCC) casos nuevos de carcinoma de células transicionales (84% de los 1.453 casos contactados) y 1271 controles hospitalarios (88% de 1.442 controles) entre junio de 1998 y junio de 2001 en 18 hospitales de las siguientes regiones en España: Barcelona, Vallès / Bages, Asturias, Alicante y Tenerife. Los sujetos de la población control tenían entre 21 y 80 años de edad en el momento del diagnóstico y residían en las zonas de influencia de los 18 hospitales participantes. De los 611 sujetos de la población control, con medidas de pH válidos disponibles, 598 (97,87%) presentaron información sobre la toma de vitaminas y el uso de medicamentos, y después de la exclusión de dos sujetos con baja calidad de la entrevista, y 175 sujetos con falta de información en alguna de las variables confusoras potenciales (consumo de verduras (n = 18), ingesta de frutas (n = 15), consumo de carne (n = 89), altura (n = 85), y/o peso (n = 70) (pudiendo haber falta de información en más de una variable en algunos sujetos), quedaron 423 individuos utilizados como población base para la elaboración del presente estudio.

Los participantes del estudio fueron entrenados para la medición de su pH urinario de forma independiente, mediante el uso de tiras reactivas dos veces al día en casa (primera orina de la mañana y por la noche antes de cenar), durante 4 días consecutivos, como mínimo dos semanas después del alta hospitalaria. Los resultados obtenidos fueron anotados en un diario, donde a su vez registraban todos los medicamentos usados en cada uno de los cuatro días en los que se llevaron a cabo las mediciones de pH.

Para estimar los efectos de los fármacos sobre el pH urinario, se calcularon los odds ratios (OR) y los intervalos de confianza (95% CI) mediante regresión logística no condicional, con dos estrategias: a) modelos forzados con todas las variables relevantes de confusión (es decir, la edad en la entrevista, el sexo, la región de estudio, la ingesta de vegetales, la ingesta de frutas, el consumo de carne, la altura, el peso, y el uso de la vitamina C), además de los medicamentos de interés, construyendo un modelo para cada medicamento según los diferentes niveles de segregación de 1, 3, 4, 5 y 7 dígitos de la clasificación ATC, y b) modelos forzados para todos los factores relevantes de confusión, combinado con

introducción de variables según estrategia “step wise” para todos los medicamentos de un mismo nivel de segregación de la clasificación ATC.

Resultados. Se encontraron asociaciones estadísticamente significativas entre algunos grupos de medicamentos utilizados por la población estudiada y su influencia en los niveles de pH de la orina: "Glucósidos Cardíacos" (OR=7.533, 95%CI: 1.63 – 34.71), fármacos que actúan sobre "Sistema Respiratorio" (OR=0.23, 95%CI: 0.07 – 0.81) y "Psicolépticos" (OR=0.35, 95%CI: 0.12 – 0.96), que en su mayoría incluyen "Ansiolíticos" (OR=0.164, 95%CI: 0.041 – 0.647).

Conclusiones. Mecanismos plausibles discutidos para explicar la asociación entre los glucósidos cardiacos y la generación de un pH de la orina constantemente ácida podrían incluir tanto el efecto de las enfermedades cardíacas subyacentes para las que estos fármacos son prescritos, como el efecto directo de los glucósidos cardíacos en el pH urinario.

La asociación entre ansiolíticos con no generar un pH en la orina constantemente ácido, sería más probable que representara el efecto de la hiperventilación generada en el transcurso de los trastornos de ansiedad para los que estos fármacos son prescritos, en lugar de un efecto directo de estos fármacos en el pH de la orina.

La asociación entre los fármacos que actúan en el Sistema Respiratorio y la no generación de un pH de la orina constantemente ácido, podría explicarse por algunos estados de enfermedades crónicas de las vías respiratorias para las que se prescriben estos fármacos, además de por el efecto directo de estos fármacos sobre el pH de la orina.

PALABRAS CLAVE: Controles, pH de la orina, carcinogénesis de vejiga, cálculos renales, medicamentos, odds ratios, orina constantemente ácida

1. Introduction

1. INTRODUCTION

ACID-BASE PHYSIOLOGY

Principles and definitions

The normal free hydrogen ion concentration in the plasma is 0.000035 – 0.000045 mEq/L. Because this concentration is so low, pH is used to describe it. pH is the negative logarithm of the free hydrogen ion concentration, shown as pH = -log [H+]. Thus, hydrogen ion (H+) concentration defines the pH of a solution.

Only free hydrogen ions, also called protons, contribute to the measured pH. If hydrogen ions are bound to other ions (such as phosphate or bicarbonate) or proteins, they are not free and do not contribute to the measured pH. Solutes and proteins that can donate or release hydrogen ions are referred to as acids, and those that can absorb or bind hydrogen ions are referred to as bases.

The normal plasma pH is about 7.30 – 7.45 and must be maintained within this narrow range for optimal physiological function. A number of physiologic processes such as (a) the metabolic enzymes that maintain adenosine triphosphate (ATP) or energy stores within cells; (b) transport proteins that move substances across cell membranes; and (c) signaling systems that transmit messages between cells or intracellular compartments, are pH-dependent, meaning they are most efficient when pH is normal. If pH levels change significantly in either the acid (lower pH, higher free H+ concentration) or alkaline (higher pH, lower free H+ concentration) direction, a number of physiologic processes required for life become altered, and the homeostatic milieu begins to deteriorate.

From a physiological perspective, the body has compartmentalized organ systems operating within specific pH ranges (Table 1).

Table 1: pH of Selected Body Tissues

Body Tissue	pH
Blood	7.35 - 7.45
Muscle	6.1
Liver	6.9
Gastric Juice	1.2 - 3.0
Salive	6.35 - 6.85
Urine	4.5 - 8.0
Pancreatic juice	7.8 - 8.0

The chemical systems that maintain a normal pH are called buffer systems, because they buffer the pH and prevent it from drifting far from normal. Each buffer system is made up of two compounds, together referred to as a buffer pair. One of the members of the pair is an acid because it is capable of donating a proton, thus lowering pH. The second member of the pair is a base, because it is capable of accepting a proton, thus raising pH.

Acid-base regulation and the kidney

It is important to understand the role of the kidneys in relationship to the lungs in the maintenance of the systemic acid-base balance (Fig. 1), to study the details of renal acid-base physiology. In a typical diet, the majority of calories are ingested in the form of carbohydrates and fats. The complete metabolism of carbohydrates and fats requires O_2 and yields CO_2 and H_2O. With normal lung function, the CO_2 produced (20 mol/day) is excreted, and there is no impact on the systemic acid-base balance. Because of the following reaction:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+ \quad (1)$$

Alterations in ventilation, by changing the pCO_2 of the blood, will alter blood pH (i.e., an increase in pCO_2 produces acidosis, whereas a decrease in Pco_2 produces alkalosis). The

metabolism of the amino acids in protein may produce either acids or alkali depending on the specific amino acid. However, the metabolism of dietary protein produces net acids (i.e., HCl of H_2SO_4). These acids, often referred to as “nonvolatile acids,” are rapidly buffered:

$$HCl + NaHCO_3 \rightarrow NaCl + CO_2 + H_2O \quad (2)$$

$$H_2SO_4 + NaHCO_3 \rightarrow Na_2SO_4 + 2CO_2 + 2H_2O \quad (3)$$

The CO_2 generated in this buffering process is excreted by the lungs, whereas the Na^+ salts of the acids are excreted by the kidneys, principally with NH_4^+ [i.e., NH_4Cl and $(NH_4)_2SO_4$]. In the process of excreting NH_4^+, HCO_3^- is generated and returned to the blood to replace the HCO_3^- lost in titrating the nonvolatile acid. This process is described later.

Other dietary constituents result in the generation of alkali. For example, when organic anions are metabolized to CO_2 and H_2O, H^+ is consumed (i.e., HCO_3^- is produced). From a dietary perspective, fruits and vegetables result in the generation of alkali, whereas meat, grains, and dairy products generate acid. In addition, the diet may contain various acids and alkalis that, when absorbed via the gastrointestinal tract, contribute to the net acid/alkali load to the body. Finally, each day, HCO_3^- is lost in the feces and thus imparts an acid load to the body. In a healthy individual consuming a “typical Western diet” (defined later in this introduction), there is a net addition of acid to the body. This acid, referred to as net endogenous acid production (NEAP), results in an equivalent loss of HCO_3^-, which must then be replaced. Importantly, the kidneys excrete acid and, in the process, generate HCO_3^-. Thus, the systemic acid-base balance is maintained when renal net acid excretion (RNAE) equals NEAP. RNAE excretion can be quantitated by measuring the excretion of NH_4^+, titratable acid (TA), and HCO_3^- (note that the excretion of H^+ is ignored, since even at a urine pH of 4.0, the concentration of H^+ = 0.1 meq/l):

$$RNAE = U_{NH4+} \times V + U_{TA} \times V - U_{HCO3^-} \times V \quad (4)$$

where U is the urine concentration and V is the urine flow rate. When a typical Western diet is ingested, NEAP is ~1 meq·kg body wt^{-1}·day^{-1}. As a consequence, RNAE must be the same.

It is important to recognize that RNAE excretion is accomplished by the transport of H^+ and HCO_3^- by the cells of the nephron. Through the action of various H^+ and HCO_3^- transporters, the kidneys reabsorb the filtered load of HCO_3^-, titrate urinary buffers, excrete NH_4^+, and acidify the urine.

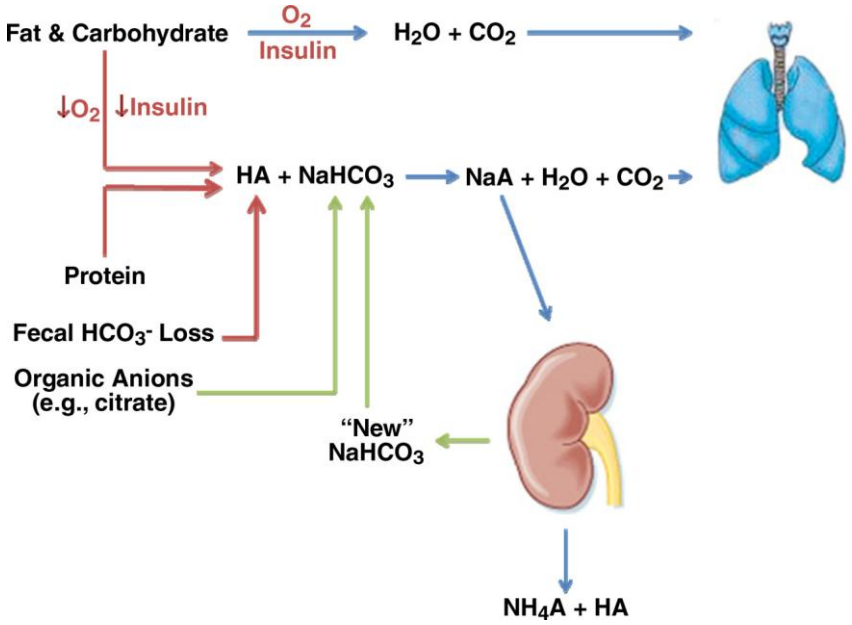

Fig. 1. Overview of the role of the kidneys in acid-base balance. See text for details. HA, nonvolatile acid. Adapted from Koeppen BM (2009)[1].

HCO_3^- Reabsorption

The cells of the nephron secrete H^+ into the tubular fluid and, in so doing, reabsorb the filtered load of HCO_3^-. The contribution of each segment of the nephron to this process is shown in Fig. 2. At a plasma HCO_3^- concentration of 24 meq/l and a glomerular filtration rate of 180 l/day, the filtered load of HCO_3^- is >4,300 meq/day. Approximately 80% of this filtered load is reabsorbed by the proximal tubule. An additional 16% is reabsorbed by the thick

ascending limb and distal convoluted tubule, and the remainder (4%) is reabsorbed by the collecting duct.

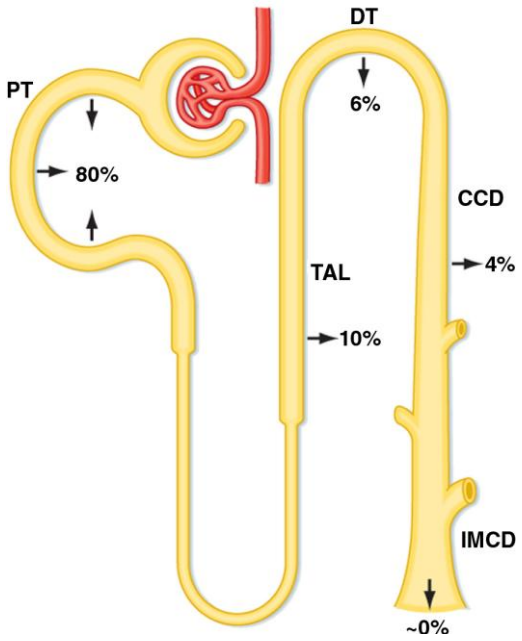

Fig. 2. Segmental HCO_3^- reabsorption. The percentage of the filtered load reabsorbed by each segment of the nephron is indicated. PT, proximal tubule; TAL, thick ascending limb of the loop of Henle; DT, distal convoluted tubule; CCD, cortical collecting duct; IMCD, inner medullary collecting duct. Adapted from Koeppen BM (2009)[1].

The cellular mechanisms by which H^+ and HCO_3^- are transported across the apical and basolateral membranes of the proximal tubule are shown in Fig. 3. H^+ secretion across the apical membrane occurs by two mechanisms. The primary mechanism is a Na^+/H^+ antiporter [Na^+/H^+ exchanger 3 (NHE3)]. It is estimated that two-thirds of proximal HCO_3^- reabsorption occurs via H^+ secretion by NHE3. Vacuolar H^+-ATPase provides another mechanism for apical H^+ secretion and is responsible for approximately one-third of HCO_3^- reabsorption.

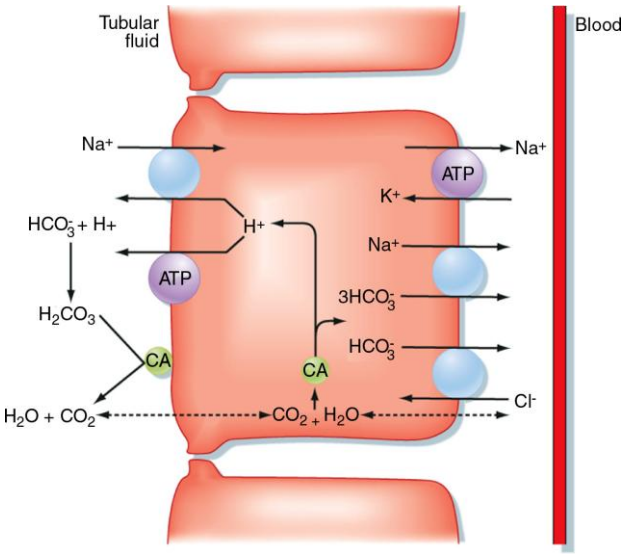

Fig. 3. Cellular mechanism for proximal tubule H^+ and HCO_3^- transport. CA, carbonic anhydrase. Adapted from Koeppen BM (2009)[1].

As shown in Fig. 3, carbonic anhydrase (CA) plays an important role in H^+ section and HCO_3^- reabsorption. Within the cell, CA-II facilitates the generation of H^+ and HCO_3^-. The H^+ is then secreted into the tubular fluid across the apical membrane, whereas the HCO_3^- exits the cell across the basolateral membrane. Membrane-bound CA (CA-IV) facilitates the production of H_2O and CO_2 from luminal carbonic acid.

Exit of HCO_3^- from the cell across the basolateral membrane occurs primarily via a $3HCO_3^-$-Na^+ symporter [the electrogenic Na^+-HCO_3^- cotransporter (NBCe1)]. There is also evidence that some HCO_3^- exits the cell in exchange for Cl^-.

The cellular mechanisms by which HCO_3^- is reabsorbed by cells of the thick ascending limb of the loop of Henle and the distal convoluted tubule are essentially the same as described above for the proximal tubule. However, some of the isoforms of the transporters are different. For example, exit of HCO_3^- from thick ascending limb cells occurs by the electroneutral Na^+-HCO_3^- symporter (NBCn1). In addition, some HCO_3^- exits these cells in exchange for Cl^- [anion exchanger 2 (AE-2)], and some by a K^+-HCO_3^- symporter. Finally,

the apical membrane Na^+/H^+ antiporter in the distal convoluted tubule may be the NHE2 isoform.

In the collecting duct, intercalated cells are responsible for H^+ and HCO_3^- transport (see Fig. 4). Acid-secreting intercalated cells have vacuolar H^+-ATPase and H^+-K^+-ATPase localized to the apical membrane, and HCO_3^- exits the cells across the basolateral membrane in exchange for Cl^- (AE-1). The less abundant HCO_3^--secreting cell has vacuolar H^+-ATPase localized to the basolateral membrane and a different Cl^-/HCO_3^- antiporter (pendrin) in the apical membrane.

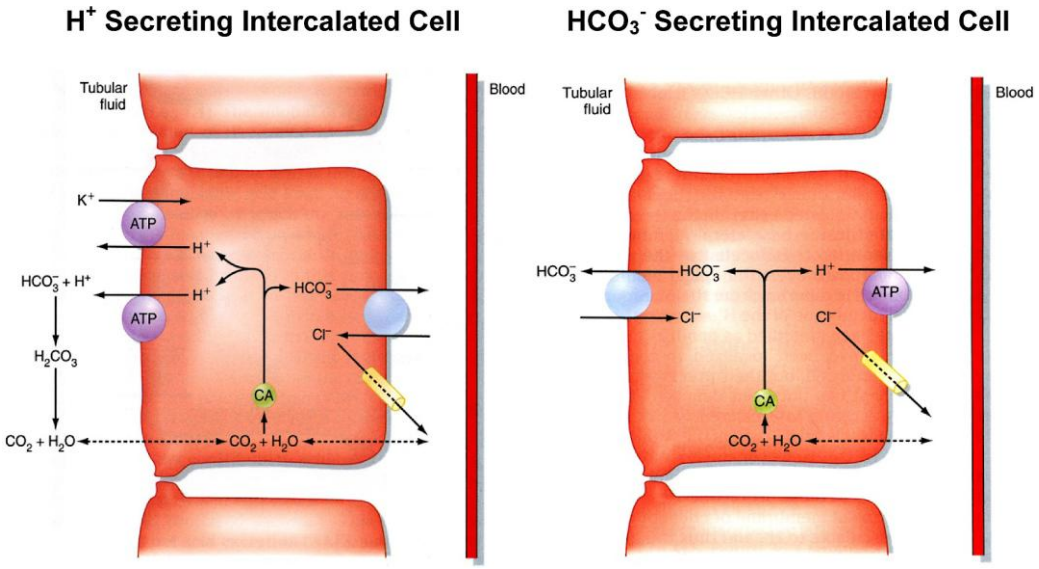

Fig. 4. Cellular mechanisms for H^+ and HCO_3^- secretion by intercalated cells of the collecting duct. Adapted from Koeppen BM (2009)[1].

Titratable Acid

The H^+ secreted into the tubular fluid can drive the reabsorption of the filtered load of HCO_3^- as just described. In addition, the secreted H^+ can combine with other luminal constituents (termed urinary buffers), such as phosphate:

$$HPO_4^{2-} + H^+ \rightarrow H_2PO_4^- \quad (5)$$

When the secreted H^+ combines with a urinary buffer, a "new HCO_3^-" is generated within the cell (see Fig. 5) and eventually replaces a HCO_3^- lost earlier in the titration of nonvolatile acids produced in cellular metabolism (NEAP). TA refers to the process whereby the kidney excretes H^+ with urinary buffers. To quantitate this process, urine is titrated with alkali to raise the normally acidic pH to that of blood. Approximately one-third of RNAE is attributed to TA, with phosphate being the predominant buffer.

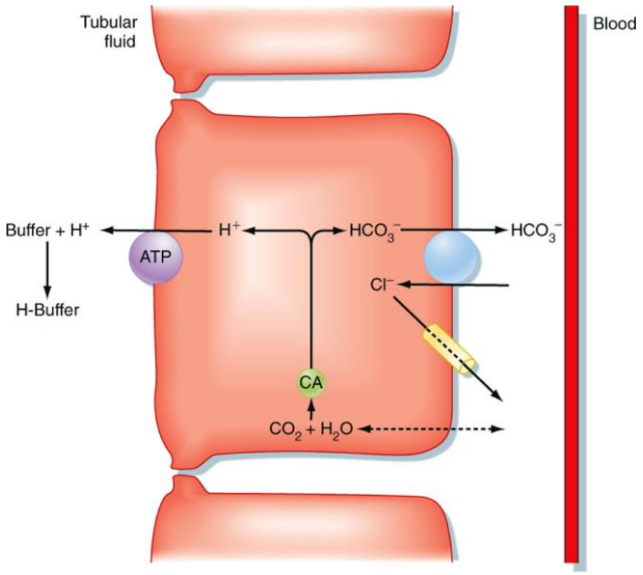

Fig. 5. Cellular mechanism for the generation of "new HCO_3^-" through the titration of urinary buffers (titratable acid). See text for details. Adapted from Koeppen BM (2009)[1].

Ammoniagenesis and NH_4^+ Excretion

An important aspect of renal acid-base physiology is the production (ammoniagenesis) and excretion of NH_4^+. Figure 6 shows this process. The kidney takes glutamine and metabolizes it to two molecules each of NH_4^+ and HCO_3^-. The NH_4^+ is excreted into the urine, and the HCO_3^-, which is "new HCO_3^-," is returned to the blood, where it replaces the HCO_3^- lost earlier in the titration of nonvolatile acids. Figure 6 also shows the fate of the NH_4^+ that is returned to the blood rather than being excreted in the urine. When this occurs, the NH_4^+ is converted to urea by the liver, and, in that process, H^+ is generated. This H^+ is buffered by HCO_3^- and thus negates the process of renal "new HCO_3^-" generation. Thus, from the perspective of renal acid-base physiology, NH_4^+ produced by the kidney must be excreted into the urine and not returned to the blood. For every milliequivalent of NH_4^+ excreted, a milliequivalent of new HCO_3^- is returned to the blood. This process accounts for approximately two-thirds of RNAE.

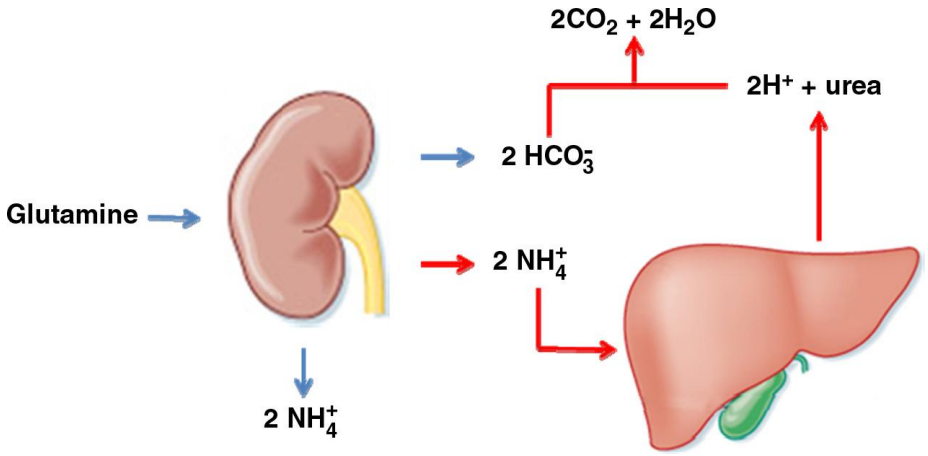

Fig. 6. General scheme for the production of HCO_3^- and NH_4^+ from the renal metabolism of glutamine. Also shown is the conversion of NH_4^+ to urea by the liver, which generates and H^+ and thus consumes HCO_3^-. See text for details. Adapted from Koeppen BM (2009)[1].

A detailed depiction of NH_4^+ handling by the nephron is shown in Fig. 7. Glutamine is metabolized by proximal tubule cells. For each molecule of glutamine metabolized, $2HCO_3^-$ and $2NH_4^+$ are produced. The HCO_3^- is returned to the blood as "new HCO_3^-," and the NH_4^+ is secreted into the tubular fluid. The majority of NH_4^+ is secreted by NHE3, with NH_4^+ substituting for H^+ on the transporter. In addition, some NH_4^+ may enter the tubular fluid as NH_3, where it is then protonated. Regardless of the mechanism, for every NH_4^+ secreted into the tubular fluid, a new HCO_3^- is returned to the blood.

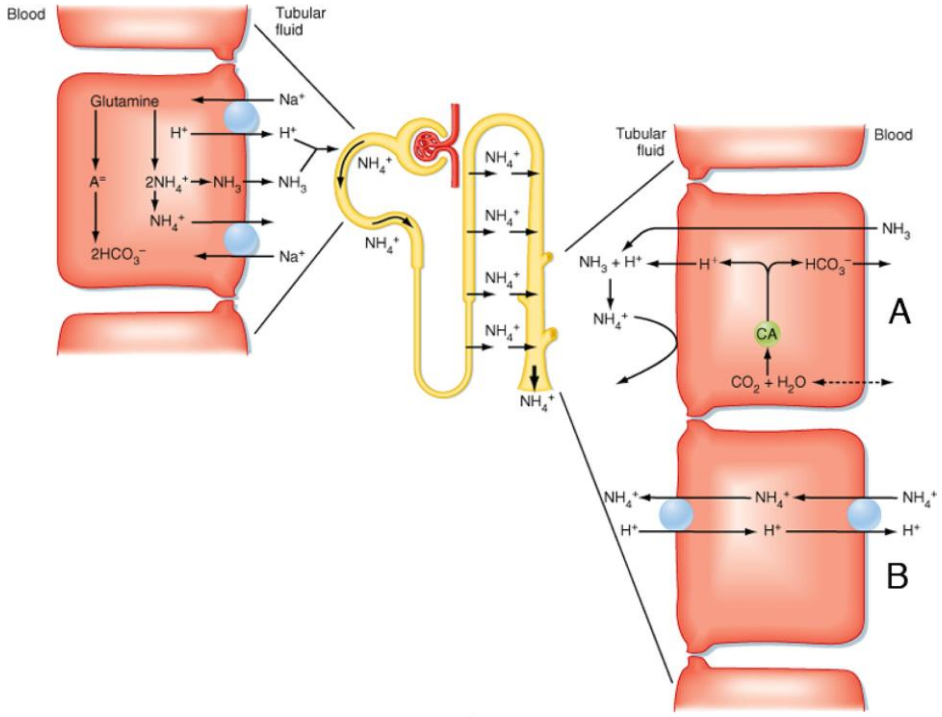

Fig. 7. Renal handling of NH_4^+. Two mechanisms for the secretion of NH_4^+ by the collecting duct are shown. *A*: nonionic diffusion and diffusion trapping of NH3. *B*: secretion of NH_4^+ via Rh glycoprotein (RhCG). See text for details. Adapted from Koeppen BM (2009)[1].

In the thick ascending limb of the loop of Henle, significant amounts of NH_4^+ are reabsorbed. Multiple routes exist for this reabsorption, including NH_4^+ substituting for K^+ on the apical membrane Na^+-K^+-$2Cl^-$ symporter (NKCC2) and movement of NH_4^+ through the paracellular pathway. NH_4^+ movement out of the cell across the basolateral membrane can occur via K^+ channels. This reabsorbed NH_4^+ accumulates in the renal medullary interstitium.

As noted above, if the NH_4^+ produced by the proximal tubule as a result of glutamine metabolism is not excreted in the urine but instead is returned to the blood, it will be metabolized to urea by the liver and, in that process, generate H^+. If this occurs, the "new HCO_3^-" generated by glutamine metabolism is negated. Thus, it is imperative that the NH_4^+ reabsorbed by the thick ascending limb of the loop of Henle be resecreted into the tubular fluid. This occurs by the collecting duct and is dependent on the ability of the collecting duct to acidify the tubular fluid.

Our understanding of the mechanism of collecting duct NH_4^+ secretion is evolving as a result of the discovery and characterization of Rh glycoproteins. Rh glycoproteins are NH_4^+ transporters similar to those found in yeast, plants, and bacteria. To date, three mammalian Rh glycoproteins have been identified, and their role in renal NH_3/NH_4^+ transport is being elucidated. RhAG is found in erythrocytes, whereas RhGB and RhGC have been localized to the kidneys (as well as other organs involved in NH_4^+ transport, such as the liver and gastrointestinal tract). RhBG is found in distal nephron segments, beginning with the distal convoluted tubule and continuing through the inner medullary collecting duct. The expression in intercalated cells is greater than in principal cells. RhCG distribution along the nephron is similar to that of RhBG, and it is present on both the apical and basolateral membranes. Importantly, chronic acidosis increases RhCG expression in the outer and inner medullary collecting ducts, and translocation of the transporter from an intracellular pool to the apical membrane (note that RhBG expression does not change with chronic acidosis). Functional studies of Rh glycoprotein have attempted to define the nature of NH_3/NH_4^+ transport, and, to date, the evidence is consistent with both electroneutral as well as electrogenic mechanisms. Evidence for Na^+-H^+ antiport also exists. Since acidification of the tubular fluid is required for NH_4^+ secretion, the operation of NH_4^+/H^+ antiporters on both the apical and basolateral membranes of collecting duct cells, as shown in Fig. 7***B***, would explain this pH-dependent NH_4^+ secretion.

The pH dependency of NH_4^+ secretion has traditionally been explained by the process of nonionic diffusion of NH_3 with diffusion trapping of NH_4^+ in the tubular fluid (see Fig. 7***A***). It remains to be determined how much of collecting duct NH_4^+ secretion occurs via this mechanism and how much is mediated by RhCG or other NH_3/NH_4^+ transporters.

After this general view of mechanisms involved in renal acid-base balance we will delve into some situations where the acidification of urine is enhanced.

Ammonia production and transport in response to acidosis

Metabolic acidosis stimulates ammonia production and transport by renal epithelial cells. Acidosis stimulates glutamine uptake into the proximal tubule and upregulates the expression of ammonia-producing enzymes, glutaminase, GDH, and PEPCK[2-5](Fig. 8). Metabolic acidosis also increases the apical NHE3 activity and protein abundance in the proximal tubule[6].

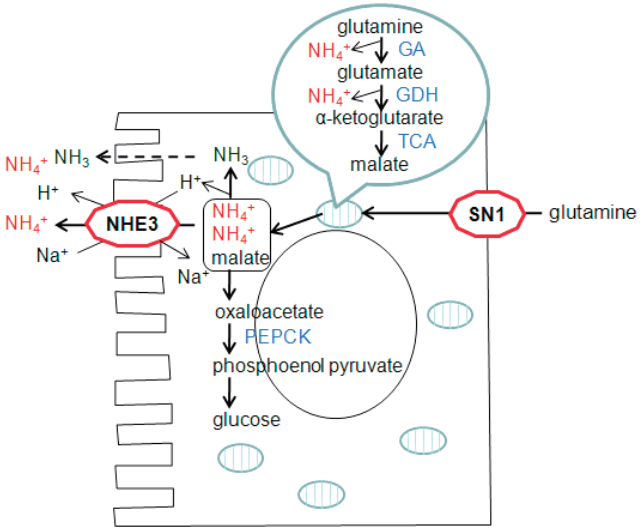

Fig. 8. Ammonia Metabolism in the Proximal Tubule. GA, glutaminase; GDH, glutamine dehydrogenase; TCA, tricarboxylic acid cycle enzymes; PEPCK, phosphoenol pyruvate carboxykinase. Adapted from Han KH (2011)[7].

Ammonia reabsorption in the thick ascending limb leads to medullary interstitial ammonia accumulation, thereby driving its secretion into the collecting duct. Metabolic acidosis

stimulated NKCC2 mRNA and protein expression in the rat and increased NHE4 mRNA expression in mouse thick ascending limb cells[8,9].

As mentioned earlier, Rh B Glycoprotein (Rhbg) and Rh C Glycoprotein (Rhcg) are recently recognized ammonia transporter family members (Fig. 9). Chronic HCl ingestion increased Rhcg protein expression and altered its subcellular distribution in the collecting duct[10,11]. Both global and collecting duct-specific Rhcg knockout mice excreted less urinary ammonia under basal conditions and developed more severe metabolic acidosis after acid loading[12,13].

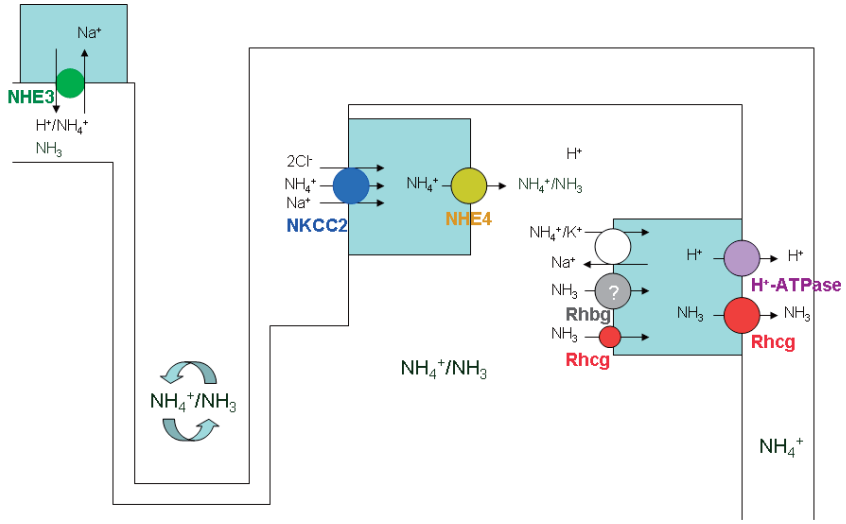

Fig. 9. Schematic Representation of the Ammonia Transport Mechanisms along the Nephron Segments. NHE3, Na+/H+ exchanger; NKCC2, Na+ - K+(NH4+) - 2Cl¯cotransporter 2; NHE4, Na+ - H+(NH4+) exchanger 4. Adapted from Han KH (2011)[7].

Ammonia production and transport in response to hypokalemia

Ammonia production and excretion into urine are also regulated by potassium balance. Hypokalemia increases renal ammonia production in experimental animals and humans, whereas hyperkalemia decreases renal ammonia production[14-16]. Renal ammonia metabolism in response to hypokalemia has not been well understood, because there is increased ammonia excretion despite the development of metabolic alkalosis.

Similar to metabolic acidosis, hypokalemia induces increased glutamine uptake into the proximal tubule and increased expression of the key ammoniagenic enzymes, glutaminase, GDH and PEPCK (see Table 2)[14,17]. Rats with Hypokalemia had a marked increase in renal NHE3 abundance[18]. However, in contrast to the metabolic acidosis, Hypokalemia downregulated NKCC2 protein expression and NHE4 mRNA expression remained unchanged[18,19].

In the collecting duct, there is increased expression of Rh glycoprotein, Rhcg, in response to hypokalemia[20]. If Rhcg expression is associated with systemic acid-base homeostasis, hypokalemia should decrease its expression due to the development of alkalosis. These observations indicate that the enhanced Rhcg expression and collecting duct ammonia excretion could be regulated through mechanisms independent of acid-base homeostasis.

The stimulation of ammoniagenesis in response to acidosis or hypokalemia is likely to be activated by either intracellular acidic pH or other factors. Recent studies have also demonstrated that the increase in urinary ammonia excretion even developed within 2 days of potassium deprivation, when the plasma potassium level was within normal limits[14].

Table 2: Expression of renal producing enzymes and transporters in response to metabolic acidosis and hypokalemia

	Acidosis	Hypokalemia
GA	↑	↑
GDH	↑	↑
PEPCK	↑	↑
NH3	↑	↑
NKCC2	↑	↓
NH4	↑	–
Rhbg	–	–
Rhcg	↑	↑

GA, glutaminase; GDH, glutamine dehydrogenase; PEPCK, phosphoenol pyruvate carboxykinase; NHE3, Na+/H+ exchanger; NKCC2, Na^+-K^+ (NH_4^+)-$2Cl^-$- cotransporter 2; NHE4, Na+-H+(NH_4^+) exchanger 4.

ACID-BASE DISORDERS INFLUENCIABLE BY MEDICATIONS

There are many disorders/diseases that lead to changes in acid base balance. These conditions are not rare or uncommon in clinical practice, but everyday occurrences on the ward or in critical care. Conditions such as asthma, chronic obstructive pulmonary disease (bronchitis or emphasaemia), diabetic ketoacidosis, renal disease or failure, any type of shock (sepsis, anaphylaxsis, neurogenic, cardiogenic, hypovolaemia), stress or anxiety which can lead to hyperventilation, and some drugs (sedatives, opoids) leading to reduced ventilation. In addition, some symptoms of disease can cause vomiting and diarrhoea, which effects acid base balance.

Management of acid–base disorders begins with accurate diagnosis, a process requiring two tasks: First, reliable measurement of acid–base variables in the blood, a complex fluid containing multiple ions and buffers; this task is an exercise in chemistry. Second, proper interpretation of the data in relation to human health and disease allowing definition of the patient's acid–base status; this is an exercise in pathophysiology. The patient's history, physical examination, and additional laboratory testing and imaging, as appropriate, then help the clinician to identify the specific cause(s) of the acid–base disturbance, and from that information to undertake appropriate intervention[21].

Assessment of acid-base status

In order to understand acid–base disorders, we must first agree on how to describe and measure it. Since Sörensen (1868–1939) first introduced the pH notation, we have used the pH scale to quantify acid–base balance. The pH scale has a tremendous advantage because it lends itself to colorimetric and electrometric techniques. There is also some physiologic relevance to the logarithmic pH scale[22]. pH is a complex variable, however. It is a nonlinear transformation of H^+ concentration – the logarithm of its reciprocal. Strictly speaking, pH can only be thought of as a dimensionless representation of H^+ concentration and is not, itself, a concentration. Indeed, pH is actually the logarithmic measure of the

volume required to contain 1 mol/l of H^+. In blood plasma at pH 7.4, this volume is approximately 25 million liters.

Regardless of how we express the concentration of H^+, either directly or as the pH, it is generally accepted that changes in blood H^+concentration occur as the result of changes in volatile [partial carbon dioxide tension (pCO_2)] and nonvolatile acids (hydrochloric, sulfuric, lactic, etc).

Since Hasselbalch adapted the Henderson equation to the pH notation of Sörenson, we have used the following Henderson–Hasselbalch equation to understand the relationship between respiratory and metabolic acid–base variables:

$$pH = pK \times \log [HCO_3 /(0.03 \times pCO_2)]$$

Clinically, we refer to changes in volatile acids as 'respiratory' and changes in nonvolatile acids as 'metabolic'. Any of the following indicators serves to identify an acid-base disorder:

1. An abnormal arterial blood pH (pH < 7.35 signifies acidemia; pH > 7.45 signifies alkalemia).
2. An arterial PCO_2 (pCO_2) that is outside the normal range (35 to 45 mm Hg).
3. A plasma HCO_3^- concentration that is outside the normal range (22 to 26 mEq/L).
4. An arterial SBE that is either abnormally high (≥ 3 mEq/L) or abnormally low (≤ -3 mEq/L).

There are three major methods of quantifying acid–base disorders, and each differs only in assessment of the 'metabolic' component. As shown on table 3, these three methods quantify the metabolic component either by using HCO_3^- (in the context of pCO_2), the standard base excess (SBE), or the strong ion difference (SID). Although there has been significant debate regarding the accuracy and utility of each method compared with the

others, all three yield virtually identical results when used to quantify the acid–base status of a given blood sample[23]. The only differences between these three approaches are conceptual (i.e., in how they approach the understanding of mechanisms)[24,25].

Table 3: Comparison of Components of Acid-Base Analysis Methods

Acid-Base Disorder	Traditional	Base Excess	Physicochemical
Respiratory acidosis	↑Pco_2	↑Pco_2	↑Pco_2
Respiratory alkalosis	↓Pco_2	↓Pco_2	↓Pco_2
Metabolic acidosis	↓HCO_3^-, anion gap	↓Base excess	↓SID, ↑Atot
Metabolic alkalosis	↑HCO_3^-	↑Base excess	↑SID

For a proper discussion of the accuracy and utility describing acid–base disorders we examine what Henderson–Hasselbalch equation tells us. An increase in pCO_2 will result in a decrease in the pH and an increase in the HCO_3^- concentration. Thus, a patient found to have a low blood pH, a condition known as acidemia, will either have an increased pCO_2 or a pCO_2 that is 'not increased'. In the former circumstance, we classify the disorder as a 'respiratory acidosis'. We use the term 'acidosis' to describe the process resulting in acidemia and 'respiratory' because the apparent cause is an increased pCO_2. This is logical, because carbonic acid results when CO_2 is added to water (or blood), and the resultant decrease in pH is entirely expected. In the latter condition pCO_2 is not increased, and thus there cannot be a respiratory acidosis. We therefore refer to this condition as 'metabolic' because some nonvolatile acid must be the cause of the acidemia. We can reverse the above logic and easily classify simple conditions of alkalemia as either resulting from respiratory or metabolic alkaloses. Thus, Henderson–Hasselbalch equation allows us to classify disorders according to the primary type of acid being increased or decreased. Over time physiology superimposes its effects on simple chemistry and the relationship between pCO_2 and HCO_3^-

is altered in order to reduce the alterations in pH. By carefully examining the changes that occur in pCO_2 and HCO_3^- in relationship to each, however, one can discern highly conserved patterns. In this way rules can be established to allow one to discover mixed disorders and to separate chronic from acute respiratory derangements. For example one such rule is the convenient formula for predicting the expected pCO_2 in the setting of a metabolic acidosis[26]:

$$pCO_2 = (1.5 \times HCO_3^-) + 8 \pm 5$$

This rule tells us what the pCO_2 should be secondary to the increase in alveolar ventilation that accompanies a metabolic acidosis. If pCO_2 does not change enough or changes too much, we classify the condition as a 'mixed' disorder, with either a respiratory acidosis if the pCO_2 is still too high, or a respiratory alkalosis if the change is too great. This rule, along with others has been recently translated to SBE terminology[23]:

$$pCO_2 = (40 + SBE) \pm 5$$

It is also very important to understand what the Henderson-Hasselbalch equation does not tell us. First, it does not allow us to discern the severity (quantity) of the metabolic derangement in a manner analogous to the respiratory component. For example, when there is a respiratory acidosis, the increase in the pCO_2 quantifies the derangement even when there is a mixed disorder. However, the metabolic component can only be approximated by the change in HCO_3^-. Second, Henderson-Hasselbalch equation does not tell us about any acids other than carbonic acid. The relationship between CO_2 and HCO_3^- provides a useful clinical 'roadmap' to guide the clinician in uncovering the etiology of an acid–base disorder as described above. The total CO_2 concentration, and hence the HCO_3^- concentration, is determined by the pCO_2, however, which is in turn determined by the balance between alveolar ventilation and CO_2 production. HCO_3^- cannot be regulated independent of pCO_2. The HCO_3^- concentration in the plasma will always increase as the pCO_2 increases, but this is not an alkalosis. To understand how the pH and HCO_3^- concentration are altered independent of pCO_2, we must look beyond Henderson and Hasselbach[27].

The traditional method relies on analysis of changes in bicarbonate concentration and the anion gap to assess the metabolic component. In general, an increased bicarbonate concentration indicates a metabolic alkalosis and a decreased bicarbonate concentration indicates a metabolic acidosis. The anion gap (AG) is used to classify metabolic acidosis into high AG or normal AG type (explained below in metabolic acidosis section).

Siggaard and Anderson developed nomograms and algorithms that form the methodology for analyzing acid-base status based on BE. Base excess quantifies the degree of metabolic acidosis or alkalosis as the amount of acid or base that must be added to a sample of whole blood in vitro to restore the pH of the sample to 7.40 while the Pco_2 is held constant at 40 mm Hg. To correct for inaccuracies when applied in vivo, BE has been modified to standardize the effect of hemoglobin and pCO_2. The standard base excess (SBE) formula is written as follows:

$SBE = 0.9287 \times (HCO_3^- - 24.4 + 14.83 \times [pH - 7.4])$, where SBE is given in mEq/L.

The SBE changes with any change in weak acid concentrations. A change in base excess describes a change in the metabolic component of acid-base status, with positive BE indicating metabolic alkalosis and negative BE indicating metabolic acidosis.

The physicochemical approach, sometimes referred to as Stewart's approach, identifies three independent variables that determine acid-base status: pCO_2, strong ion difference (SID), and total nonvolatile weak acids[28,29]. These variables also determine changes in dependent variables, such as pH, HCO_3^-, CO_3^{2-}, OH^- and H^+. The SID is the difference between the sum of all strong cation concentrations and the sum of all strong anion concentrations. All concentrations must be expressed in mEq/L. The formula for calculating SID (in mEq/L) is as follows:

$SID = [Na^+ + K^+ + Ca^{2+} + Mg^{2+}] - [Cl^- + Lactate]$.

Attempts to identify which method of acid-base analysis is most correct or most clinically useful have resulted in numerous debates and studies[30-32].

The clinician should integrate the analysis of the acid-base status with the patient's clinical history and additional testing results when determining the most appropriate interventions. Analysis of acid-base status in a critically ill patient at a single point in time provides only a snapshot of a complex and rapidly changing environment.

Metabolic Acid-Base Disorders

Metabolic acid-base derangements are produced by a significantly greater number of underlying disorders than respiratory disorders are, and they are almost always more difficult to treat. Traditionally, metabolic acidosis and alkalosis are categorized according to the ions that are responsible (i.e., lactic acidosis and chloride-responsive alkalosis). Metabolic acidosis are corrected by increasing the plasma Na^+ concentration more than the plasma Cl^- concentration (i.e., by administering $NaHCO_3$), and metabolic alkalosis are corrected by replacing lost Cl^- [i.e., by giving sodium chloride (NaCl), potassium chloride (KCl), or even hydrochloric acid (HCl)]. So-called chloride-resistant metabolic alkaloses (*see* Metabolic Alkalosis, Chloride-Resistant Alkalosis, *below)* are resistant to chloride administration only because of ongoing renal Cl^- loss that increases in response to increased Cl^- replacement (as with hyperaldosteronism).

Pathophysiology

Disorders of metabolic acid-base balance occur in one of three ways: (1) as a result of dysfunction of the primary regulating organs, (2) as a result of exogenous administration of drugs or fluids that alter the body's ability to maintain normal acid-base balance, or (3) as a result of abnormal metabolism that overwhelms the normal defense mechanisms. The organ systems responsible for regulating in both health and disease are the renal system and, to a lesser extent, the gastrointestinal tract.

Metabolic Acidosis

Traditionally, metabolic acidosis are categorized according to the presence or absence of unmeasured anions. These unmeasured anions are routinely detected by examining the plasma electrolytes and calculating the anion gap (AG) (see below).

Even extreme acidosis appears to be well tolerated by healthy persons, particularly when the duration of the acidosis is short. For example, healthy individuals may achieve an arterial pH lower than 7.15 and a lactate concentration higher than 20 mEq/L during maximal exercise, with no lasting effects[33]. Over the long term, however, even mild acidemia (pH < 7.35) may lead to metabolic bone disease and protein catabolism. Furthermore, critically ill patients may not be able to tolerate even brief episodes of acidemia. There do appear to be significant differences between metabolic and respiratory acidosis with respect to patient outcome, and these differences suggest that the underlying disorder may be more important than the absolute degree of acidemia[34].

If prudence dictates that symptomatic therapy is to be provided, the likely duration of the disorder should be taken into account. When the disorder is expected to be a short-lived one (i.e., diabetic ketoacidosis), maximizing respiratory compensation is usually the safest approach. Once the disorder resolves, ventilation can be quickly reduced to normal levels, and there will be no lingering effects from therapy (i.e., by administering $NaHCO_3$, there is a risk of alkalosis when the underlying disorder resolves). When the disorder is likely to be a more chronic one (i.e., renal failure), therapy is indicated. If increasing the plasma Na^+ concentration is inadvisable for other reasons (i.e., hypernatremia), $NaHCO_3$ administration is inadvisable. It is noteworthy that $NaHCO_3$ administration has not been shown to improve outcome in patients with lactic acidosis[35]. In addition, $NaHCO_3$ administration is associated with certain disadvantages. Large (hypertonic) doses, if given rapidly, may actually reduce blood pressure[36] and may cause sudden, severe increases in pCO_2[37]. Accordingly, it is important to assess the patient's ventilatory status before $NaHCO_3$ is administered,

particularly if the patient is not on a ventilator. $NaHCO_3$ infusion also affects serum K^+ and Ca^{2+} concentrations, which must be monitored closely.

To avoid some of the disadvantages of $NaHCO_3$ therapy, alternative therapies for metabolic acidosis have been developed. Carbicarb is an equimolar mixture of sodium carbonate (Na_2CO_3) and $NaHCO_3$[38]. Like $NaHCO_3$, carbicarb works by increasing the plasma Na^+ concentration, except that it does not raise the pCO_2. THAM (*tris*-hydroxymethyl aminomethane) is a synthetic buffer that consumes CO_2 and readily penetrates cells[39]. It is a weak base (pK = 7.9) and, as such, is unlike other plasma constituents. Although THAM has been available since the 1960s, there is surprisingly little information available regarding its efficacy in humans with acid-base disorders. In small uncontrolled studies, THAM appears to be capable of reversing metabolic acidosis secondary to ketoacidosis or renal failure without causing obvious toxicity; however, adverse reactions have been reported, including hypoglycemia, respiratory depression, and even fatal hepatic necrosis, when concentrations exceeding 0.3 mol/L are used. In Europe, a mixture of THAM, acetate, $NaHCO_3$, and disodium phosphate is available. This mixture, known as tribonate (Tribonat; Pharmacia & Upjohn, Solna, Sweden), seems to have fewer side effects than THAM alone does, but as with THAM, experience with its use in humans is still quite limited.

Anion Gap

Determination and utility of anion gap

The AG has been used by clinicians for more than 30 years and has evolved into a major tool for evaluating acid-base disorders[40]. It is calculated—or, rather, estimated—from the difference between the routinely measured concentrations of serum cations (Na^+ and K^+) and the routinely measured concentrations of anions (Cl^- and HCO_3^-). Normally, albumin accounts for the bulk of this difference, with phosphate playing a lesser role. Sulfate and lactate also contribute a small amount to the gap (normally, < 2 mEq/L); however, there are also unmeasured cations (e.g., Ca^{2+} and Mg^{2+}), which tend to offset the effects of sulfate and

lactate except when the concentration of either one is abnormally increased. Plasma proteins other than albumin can be either positively or negatively charged, but in the aggregate, they tend to be electrically neutral[41], except in rare cases of abnormal paraproteins (as in multiple myeloma). In practice, the AG is calculated as follows:

$AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$

The primary value of the AG is that it quickly and easily limits the differential diagnosis in a patient with metabolic acidosis. When the AG is increased, the explanation is almost invariably one of the following five disorders: ketosis, lactic acidosis, poisoning, renal failure, and sepsis. In addition to these disorders, however, there are several conditions that can alter the accuracy of AG estimation and are particularly frequent in critical illness[42,43].

The primary problem with the AG is its reliance on the use of a supposedly normal range produced by albumin and, to a lesser extent, phosphate. Concentrations of albumin and phosphate may be grossly abnormal in patients with critical illness, and these abnormalities may change the normal AG range in this setting. Thus, the normal AG for a given patient can be conveniently estimated as follows[27]:

Normal AG = 2(albumin [g/dl]) + 0.5(phosphate [mg/dl])

Most common causes for metabolic acidosis are resumed in Table 4.

Table 4: Causes of metabolic acidic disorders (normal vs elevated anion gap)

Elevated Anion Gap (>16 meq)	Normal Anion Gap (8-16 meq)
Increased Endogenous production: Ketoacidosis (Alcohol, Starvation, DKA) Lactic Acidosis	**Loss of Bicarbonate:** Diarrhea Carbonic anhydrase inhibitors Type 2 RTA (proximal) Pancreatic ileostomy Pancreatic, biliary, intestinal fistula
	Exogenous Administration: ammonium chloride or HCL
Uremia	**Decreased Renal Acid Excretion:** Type 1(distal) ,4 RTA Renal Failure
Intoxications: Methanol, Ethylene Glycol, Paraldehyde, Salicylates, INH	**Miscellaneous:** Hyperkalemia Recovery from DKA (diabetic ketoacidosis)

Positive-Anion Gap Acidosis

Lactic acidosis

In basic terms, lactic acid is the normal endpoint of the anaerobic breakdown of glucose in the tissues. The lactate exits the cells and is transported to the liver, where it is oxidized back to glucose. In the setting of decreased tissue oxygenation, lactic acid is produced as the anaerobic cycle is utilized for energy production. With a persistent oxygen debt and overwhelming of the body's buffering abilities (whether from chronic dysfunction or excessive production), lactic acidosis ensues[44,45].

Medicinal and toxic causes of lactic acidosis include the following: Acetaminophen, alcohols and glycols (ethanol, ethylene glycol, methanol, propylene glycol), antiretroviral nucleoside

analogs (zidovudine, didanosine, lamivudine), beta-adrenergic agents (epinephrine, ritodrine, terbutaline), biguanides (phenformin, metformin), cocaine, cyanogenic compounds (cyanide, aliphatic nitriles, nitroprusside), diethyl ether, 5-Fluorouracil, halothane, iron, isoniazid, propofol, sugars and sugar alcohols (fructose, sorbitol, and xylitol), salicylates, strychnine, sulfasalazine and valproic acid.

A 2010 study by Salpeter et al found that the oral antihyperglycemic agent metformin, despite concerns to the contrary, is not associated with an increased risk for lactic acidosis compared with other antihyperglycemic treatments[46].

Ketoacidosis

Ketoacidosis is a metabolic state associated with high concentrations of ketone bodies, formed by the breakdown of fatty acids and the deamination of amino acids. The two common ketones produced in humans are acetoacetic acid and β-hydroxybutyrate. The pathological metabolic state is marked by extreme and uncontrolled ketosis. In ketoacidosis, the body fails to adequately regulate ketone production causing such a severe accumulation of keto acids that the pH of the blood is substantially decreased. In extreme cases ketoacidosis can be fatal.

Ketoacidosis is most common in untreated type 1 diabetes mellitus, when the liver breaks down fat and proteins in response to a perceived need for respiratory substrate. Prolonged alcoholism may lead to alcoholic ketoacidosis.

Acidosis secondary to renal failure

Although renal failure may produce a hyperchloremic metabolic acidosis, especially when it is chronic, the buildup of sulfates and other acids frequently increases the AG; however, the increase usually is not large[47]. Similarly, uncomplicated renal failure rarely produces severe acidosis, except when it is accompanied by high rates of acid generation (i.e., from hypermetabolism).

Acidosis secondary to toxin ingestion

Metabolic acidosis with an increased AG is a major feature of various types of intoxication (see Table 4). Generally, it is more important to recognize these conditions and provide specific therapy for them than it is to treat the acid-base imbalances that they produce.

Acidosis secondary to rhabdomyolysis

The extensive muscle tissue breakdown associated with myonecrosis may also be a source of metabolic acidosis. In this situation, the acidosis results from accumulation of organic acids. The myoglobinuria associated with the disorder may also induce renal failure. In most cases, the diagnosis is a clinical one and can be facilitated by measuring creatinine kinase or aldolase levels. Early identification and aggressive resuscitation may prevent the onset of renal failure and improve the prognosis[48].

Acidosis of unknown origin

Several causes of an increased AG have been reported that have yet to be elucidated. An unexplained AG in the nonketotic hyperosmolar state of diabetes has been reported[49]. In addition, even when very careful measurement techniques have been employed, unmeasured anions have been reported in the blood of patients with sepsis[50,51], patients with liver disease[52], and animals to which endotoxin had been administered[53]. Furthermore, unknown cations also appear in the blood of some critically ill patients[51]. The significance of these findings remains to be determined.

Non-Anion Gap (Hyperchloremic) Acidoses

Hyperchloremic metabolic acidosis occurs as a result of either an increase in the level of Cl^- relative to the levels of strong cations (especially Na^+) or a loss of cations with retention of Cl^-. The various causes of such an acidosis can be distinguished on the basis of the history and the measured Cl^- concentration in the urine. When acidosis occurs, the kidney

normally responds by increasing Cl^- excretion; the absence of this response identifies the kidney as the source of the problem. Extrarenal hyperchloremic acidoses occur because of exogenous Cl^- loads (iatrogenic acidosis) or because of loss of cations from the lower GI tract without proportional loss of Cl^- (gastrointestinal acidosis).

Renal tubular acidosis

Renal tubular acidosis (RTA) is a medical condition that involves an accumulation of acid in the body due to a failure of the kidneys to appropriately acidify the urine[54]. When blood is filtered by the kidney, the filtrate passes through the tubules of the nephron, allowing for exchange of salts, acid equivalents, and other solutes before it drains into the bladder as urine. The metabolic acidosis that results from RTA may be caused either by failure to recover sufficient (alkaline) bicarbonate ions from the filtrate in the early portion of the nephron (proximal tubule) or by insufficient secretion of (acid) hydrogen ions into the latter portions of the nephron (distal tubule).

Gastrointestinal acidosis

Fluid secreted into the gut lumen contains more Na^+ than Cl^-; the proportions are similar to those seen in plasma. Massive loss of this fluid, particularly if lost volume is replaced with fluid containing equal amounts of Na^+ and Cl^-, will result in a decreased plasma Na^+ concentration relative to the Cl^- concentration.

Iatrogenic acidosis

Two of the most common causes of a hyperchloremic metabolic acidosis are iatrogenic, and both involve administration of Cl^-. One of these potential causes is parenteral nutrition. Modern parenteral nutrition formulas contain weak anions (i.e., acetate) in addition to Cl^-, and the proportions of these anions can be adjusted according to the acid-base status of the patient. If sufficient amounts of weak anions are not provided, the plasma Cl^-

concentration will increase causing acidosis. The other potential cause is fluid resuscitation with saline, which can give rise to a so-called dilutional acidosis (a problem first described more than 40 years ago)[55].

Unexplained hyperchloremic acidosis

Critically ill patients sometimes manifest hyperchloremic metabolic acidosis for reasons that cannot be determined. Often, other coexisting types of metabolic acidosis are present, making the precise diagnosis difficult. For example, some patients with lactic acidosis have a greater degree of acidosis than can be explained by the increase in the lactate concentration[50], and some patients with sepsis and acidosis have normal lactate levels[56]. In many instances, the presence of unexplained anions is the cause[50-52], but in other cases, there is a hyperchloremic acidosis.

Metabolic Alkalosis

Metabolic alkalosis occurs as a result of decrease of anions (i.e., Cl^- from the stomach and albumin from the plasma) or increases in cations (rare). Metabolic alkalosis can be divided into those in which Cl^- losses are temporary and can be effectively replaced (chloride-responsive alkalosis) and those in which hormonal mechanisms produce ongoing losses that, at best, can be only temporarily offset by Cl^- administration (chloride-resistant alkalosis). Like hyperchloremic acidosis, metabolic alkalosis can be confirmed by measuring the urine Cl^- concentration (see Table 5).

Table 5: Differential diagnosis for metabolic alkalosis. Adapted from Kellum et al (2006)

Chloride loss ($Cl^- < Na^+$)	Chloride-responsive alkalosis (urine Cl^- concentration < 10 mmol/L) GI loss Vomiting Gastric drainage Chloride-wasting diarrhea (villous adenoma) Diuretic use Hypercapnia Chloride-resistant alkalosis (urine Cl^- concentration > 20 mmol/L) Mineralocorticoid excess Primary hyperaldosteronism (Conn syndrome) Secondary hyperaldosteronism Cushing syndrome Liddle syndrome Bartter syndrome Exogenous corticoids Excessive licorice intake Ongoing diuretic use
Exogenous sodium load ($Na^+ > Cl^-$)	Sodium salt administration (acetate, citrate) Massive blood transfusions Parenteral nutrition Plasma volume expanders Sodium lactate (Ringer solution)
Other	Severe deficiency of intracellular cations (Mg^{2+}, K^+)

Chloride-Responsive Alkalosis

Chloride-responsive metabolic alkalosis usually occurs as a result of loss of Cl^- from the stomach (i.e., through vomiting or gastric drainage). Treatment consists of replacing the lost Cl^-, either slowly (with NaCl) or relatively rapidly (with KCl or even HCl). Because chloride-responsive alkalosis is usually accompanied by volume depletion, the most common therapeutic choice is to give saline along with KCl. Dehydration stimulates aldosterone secretion, which results in reabsorption of Na^+ and loss of K^+. Saline is effective even though it contains Na^+ because the administration of equal amounts of Na^+ and Cl^- yields a larger relative increase in the Cl^- concentration than in the Na^+ concentration.

Diuresis and other forms of volume contraction cause metabolic alkalosis mainly by stimulating aldosterone secretion; however, diuretics also directly stimulate excretion of K^+ and Cl^-, further complicating the problem and inducing metabolic alkalosis more rapidly.

Chloride-Resistant Alkalosis

Chloride-resistant alkalosis is characterized by an increased urine Cl^- concentration (> 20 mmol/L) and ongoing Cl^- loss that cannot be abolished by Cl^- replacement. Most commonly, the proximate cause is increased mineralocorticoid activity. Treatment involves identification and correction of the underlying disorder.

Respiratory Acid-Base Disorders

Respiratory disorders are far easier to diagnose and treat than metabolic disorders are because the mechanism is always the same, even though the underlying disease process may vary. CO_2 is produced by cellular metabolism or by the titration of HCO_3^- by metabolic acids. Normally, alveolar ventilation is adjusted to maintain the pCO_2 between 35 and 45 mm Hg. When alveolar ventilation is increased or decreased out of proportion to the pCO_2, a respiratory acid-base disorder exists.

Pathophysiology

CO_2 is produced by the body at a rate of 220 ml/min, which equates to production of 15 mol/L of carbonic acid each day. By way of comparison, total daily production of all the nonrespiratory acids managed by the kidney and the gut amounts to less than 500 mmol/L. Pulmonary ventilation is adjusted by the respiratory center in response to pCO_2, pH, and pO_2, as well as in response to exercise, anxiety, wakefulness, and other signals. Normal pCO_2 (40 mm Hg) is attained by precisely matching alveolar ventilation to metabolic CO_2 production. pCO_2 changes in predictable ways as a compensatory ventilatory response to the altered arterial pH produced by metabolic acidosis or alkalosis.

Respiratory Acidosis

When the rate of CO_2 elimination is inadequate relative to the rate of tissue CO_2 production, the pCO_2 rises to a new steady state, determined by the new relation between alveolar ventilation and CO_2 production. In the short term, this rise in the pCO_2 increases the concentrations of both H^+ and HCO_3^- according to the carbonic acid equilibrium equation. Thus, the change in the HCO_3^- concentration is mediated not by any systemic adaptation but by chemical equilibrium. The higher HCO_3^- concentration does not buffer the H^+ concentration. The SID does not change, nor does the SBE. Tissue acidosis always occurs in respiratory acidosis because CO_2 inevitably builds up in the tissue.

If the pCO_2 remains elevated, a compensatory response will occur, to return the H^+ concentration to the normal range, by removing Cl^- from the plasma space. If Cl^- moves into tissues or red blood cells, it will result in intracellular acidosis (complicated by the elevated tissue pCO_2); thus, to exert a lasting effect, Cl^- must be removed from the body. The kidney is designed to do this, whereas the GI tract is not (though the adaptive capacity of the GI tract as a route of Cl^- elimination has not been fully explored). Accordingly, patients with renal disease have a very difficult time adapting to chronic respiratory acidosis.

Patients whose renal function is intact can eliminate Cl^- in the urine; after a few days, and the pH is restored to a value of 7.35. It is unclear whether this amount of time is necessary because of the physiologic constraints of the system or because the body benefits from not being overly sensitive to transient changes in alveolar ventilation. In any case, this response yields an increased pH for any degree of hypercapnia. According to the Henderson-Hasselbalch equation, the increased pH results in an increased HCO_3^- concentration for a given pCO_2. Thus, the 'adaptive' increase in the HCO_3^- concentration is actually the consequence, not the cause, of the increased pH. As said before (see above), only changes in the independent variables of acid-base balance (pCO_2, strong ion difference (SID), and

total nonvolatile weak acids) can affect the plasma H^+ concentration, and HCO_3^- concentration is not an independent variable.

Respiratory Alkalosis

Respiratory alkalosis may be the most frequently encountered acid-base disorder. It occurs in residents of high-altitude locales and in persons with any of a wide range of pathologic conditions, the most important of which are salicylate intoxication, early sepsis, hepatic failure, and hypoxic respiratory disorders. Respiratory alkalosis also occurs in association with pregnancy and with pain or anxiety. Hypocapnia appears to be a particularly strong negative prognostic indicator in patients with critical illness. Like acute respiratory acidosis, acute respiratory alkalosis results in a small change in the HCO_3^- concentration, as dictated by the Henderson-Hasselbalch equation. If hypocapnia persists, the SID begins to decrease as a consequence of renal Cl^- reabsorption. After 2 to 3 days, the SID assumes a new and lower steady state[57].

Severe alkalemia is unusual in respiratory alkalosis. Management therefore is typically directed toward the underlying cause. In general, these mild acid-base changes are clinically important more for what they can alert the clinician to, in terms of underlying disease, than for any direct threat they pose to the patient. In rare cases, respiratory depression with narcotics is necessary.

URINE pH

Overview

Urine is a typically sterile liquid by-product of the body secreted by the kidneys through a process called urination and excreted through the urethra. Cellular metabolism generates numerous by-products, many rich in nitrogen, that require elimination from the bloodstream. These by-products are eventually expelled from the body in a process known as micturition, the primary method for excreting water-soluble chemicals from the body. These chemicals can be detected and analyzed by urinalysis.

Most animals have excretory systems for elimination of soluble toxic wastes. In humans, soluble wastes are excreted primarily by the urinary system and, to a lesser extent in terms of urea removed, by perspiration. The urinary system consists of the kidneys, ureters, urinary bladder, and urethra. The system produces urine by a process of filtration, reabsorption, and tubular secretion. The kidneys extract the soluble wastes from the bloodstream, as well as excess water, sugars, and a variety of other compounds. The resulting urine contains high concentrations of urea and other substances, including toxins. Urine flows from the kidney through the ureter, bladder, and finally the urethra before passing from the body.

Urine pH is used to classify urine as either a dilute acid or base solution. Seven is the point of neutrality on the pH scale. The glomerular filtrate of blood is usually acidified by the kidneys from a pH of approximately 7.4 to a pH of about 6 in the urine. Depending on the person's acid-base status, the pH of urine may range from 4.5 to 8.

The kidneys maintain normal acid-base balance primarily through the reabsorption of sodium and the tubular secretion of hydrogen and ammonium ions. Urine becomes increasingly acidic as the amount of sodium and excess acid retained by the body increases. Alkaline urine, usually containing bicarbonate-carbonic acid buffer, is normally excreted when there is

an excess of base or alkali in the body. Secretion of acid or alkaline urine by the kidneys is one of the most important mechanisms that the body uses to maintain a constant body pH.

External factors influencing urine pH

Several researchers have noted that the contemporary Western diet has increased in net acid load relative to diets of the ancestral pre-agricultural *Homo sapiens*[58-60].

Quite possibly, this shift occurred because of the agricultural revolution and the ubiquity of processed grains and shelf-stable food products devoid of essential nutritional components. In addition to this underlying foundational change in diet, there is the overlay of various nutritional fads that have risen and fallen over the past few decades. Most recently, the latest diet trend has been an interest in high-protein foods accompanied by a compensatory decrease in the phytochemical load from fresh fruits and vegetables. Indeed, high-protein diets increase net dietary acid load and acidify the urine pH.[59-62]

Several factors can influence on urine pH: diet, body surface area, acute water load and exercise[63,64] (through lactic acidosis). Exposures to these factors cause fluctuations in urine pH during the course of a 24 hours period[63,65,66]. Remer and Manz calculated the potential renal acid loads of certain food groups and reported that alkaline-forming foods were primarily vegetable and fruits, whereas acid-forming foods were derived from cheese, meat, fish, and grain products[61] (see Table 6).

Table 6: Assessment of dietary effects on acid-base balance (Adapted and modified from Remer T, Manz F (1995) and Remer et al. (2003))

Foodstuffs with a negative value (milliequivalents per 100 g) exert a base (B) effect, foodstuffs with a positive value an acid (A) effect. Neutral foodstuffs are labelled with N.

*PRAL (Potential renal acid load) = mEq of Cl + PO4 + SO4 – Na – K – Ca – Mg)

Food	PRAL* (mEq/100g)		Food	PRAL* (mEq/100g)	
Beverages			**Fish & Seafood**		
Apple juice, unsweetened	B	-	Carp	A	7.9
Beer, draft	B	-	Cod, fillets	A	7.1
Beer, pale	A		Eal, smoked	A	11.0
Beer, stout	B	-	Haddock	A	6.8
Beetroot juice	B	-	Halibut	A	7.8
Carrot juice	B	-	Herring	A	7.0
Coca-Cola	A		Mussels	A	15.3
Cocoa, made with semi-skimmed milk	B	-	Prawn	A	15.5
Coffee, infusion, 5 minutes	B	-	Rose-fish	A	10.0
Espresso	B	-	Salmon	A	9.4
Fruit tea, infusion	B	-	Salted matie (herring)	A	8.0
Grape juice	B	-	Sardines in oil	A	13.5
Grape juice, unsweetened	B	-	Shrimps	A	7.6
Green tea, infusion	B	-	Sole	A	7.4
Herbal tea	B	-	Tiger Prawn	A	18.2
Lemon juice	B	-	Trout, steamed	A	10.8
Mineral water (Apollinaris)	B	-	Zander	A	7.1
Mineral water (Volvic)	B	-			
Orange juice, unsweetened	B	-	**Fruits**		
Red wine	B	-	Apples	B	-2.2
Tea, Indian, infusion	B	-	Apricots	B	-4.8
Tomato juice	B	-	Bananas	B	-5.5
Vegetable juice (Tomato, beetroot, carrot)	B	-	Black currants	B	-6.5
White wine, dry	B	-	Cherries	B	-3.6
			Figs, dried	B	-18.1
Fats & Oil			Grapefruit	B	-3.5
Butter	A	0.6	Grapes	B	-3.9
Margarine	B	-0.5	Kiwi fruit	B	-4.1
Olive oil	N	0.0	Lemon	B	-2.6
Sunflower seed oil	N	0.0	Mango	B	-3.3
			Orange	B	-2.7
Nuts			Peach	B	-2.4
Hazelnuts	B	-	Pear	B	-2.9
Peanuts, plain	S		Pineapple	B	-2.7
Pistachio	S		Raisins	B	-21.0
Sweet almonds	S		Strawberries	B	-2.2
Walnuts	S		Watermelon	B	-1.9

Cereals & Flour		
Amaranth	A	7.5
Barley (wholemeal)	A	5.0
Buckwheat (whole grain)	A	3.7
Corn (whole grain)	A	3.8
Cornflakes	A	6.0
Dried unripe spelt grains (wholemeal)	A	8.8
Dried unripe spelt grains (wholemeal)	A	8.8
Millet (whole grain)	A	8.6
Oat flakes	A	10.7
Rice, brown	A	12.5
Rice, white	A	4.6
Rice, white, boiled	A	1.7
Rye flour	A	4.4
Rye flour, wholemeal	A	5.9
Wheat flour, white	A	6.9
Wheat flour, wholemeal	A	8.2

Pastries	
Macaroni	A
Noodles	A
Spaetzle (German sort of pasta)	A
Spaghetti, white	A
Spaghetti, wholemeal	A

Bread	
Bread, rye flour	A
Bread, rye flour, mixed	A
Bread, wheat flour, mixed	A
Bread, wheat flour, whole meal	A
Bread, white wheat	A
Coarse wholemeal bread	A
Crispbread, rye	A
Pumpernickel	A
Rusk	A
Wholemeal bread	A

Peas & Beans		
Beans, green / French beans	B	-3.1
Lentils, green and brown, whole, dried	A	3.5
Peas	A	1.2

Meat & Sausages	
Beef, lean only	A
Cervelat sausage	A
Chasseur sausage	A
Chicken, meat only	A
Corned beef, canned	A
Duck	A
Duck, lean only	A	8.4
Frankfurters	A	6.7
Goose, lean only	A	13.0
Lamb, lean only	A	7.6
Liver (veal)	A	14.2
Liver sausage	A	10.6
Luncheon meat, canned	A	10.2
Ox liver	A	15.4
Pig's Liver	A	15.7
Pork sausage	A	7.0
Pork sausage (Wiener)	A	7.7
Pork, lean only	A	7.9
Rabbit, lean only	A	19.0
Rump steak, lean and fat	A	8.8
Salami	A	11.6
Slicing sausage containing ham	A	8.3
Turkey, meat only	A	9.9
Veal, fillet	A	9.0

Milk, Dairy products & Eggs		
Buttermilk	A	0.5
Camembert	A	14.6
Cheddar-type, reduced fat	A	26.4
Cottage cheese, plain	A	8.7
Cream, fresh, sour	A	1.2
Curd cheese	A	0.9
Edam Cheese full fat	A	19.4
Egg, chicken, whole	A	8.2
Egg, white	A	1.1
Egg, yolk	A	23.4
Emmental Cheese full fat	A	21.1
Fresh cheese (Quark)	A	11.1
Full-fat soft cheese	A	4.3
Gouda	A	18.6
Hard cheese	A	19.2
Kefir Cheese full fat	N	0.0
Milk, whole, evaporated	A	1.1
Milk, whole, pasteurised and sterilized	A	0.7
Parmesan	A	34.2
Processed cheese, plain	A	28.7
Rich creamy full fat cheese	A	13.2
Skimmed Milk	A	0.7
Whey	B	-1.6
Yogurt, whole milk, fruit	A	1.2
Yogurt, whole milk, plain	A	1.5

Sweats		
Chocolate, bitter	A	0.4
Chocolate, milk	A	2.4
Honey	B	-0.3
Ice cream, dairy, vanilla	A	0.6
Ice cream, fruit, mixed	B	-0.6
Madeira cake	A	3.7
Marmalade	B	-1.5
Nougat hazelnut cream	B	-1.4
Sugar, brown	B	-1.2
Sugar, white	N	0.0

Vegetables		
Asparagus	B	-0.4
Broccoli, green	B	-1.2
Brussel sprouts	B	-4.5
Carrots	B	-4.9
Cauliflower	B	-4.0
Celery	B	-5.2
Chicory	B	-2.0
Cucumber	B	-0.8
Eggplant	B	-3.4
Fennel	B	-7.9
Garlic	B	-1.7
Gherkin, pickled	B	-1.6
Kale	B	-7.8
Kohlrabi	B	-5.5
Lamb's lettuce	B	-5.0
Leeks	B	-1.8
Lettuce	B	-2.5
Lettuce, iceberg	B	-1.6
Mushrooms, common	B	-1.4
Onions	B	-1.5
Peppers, Capsicum, green	B	-1.4
Potatoes	B	-4.0
Radish, red	B	-3.7
Rocket salad	B	-7.5
Sauerkraut	B	-3.0
Soy beans	B	-3.4
Soy milk	B	-0.8
		-
Spinach	B	14.0
Tofu	B	-0.8
Tomato	B	-3.1
Zucchini	B	-4.6

Herbs & Vinegar		
Apple vinegar	B	-2.3
Basil	B	-7.3
Chives	B	-5.3
Parsley	B	-12.0
Wine vinegar, balsamic	B	-1.6

Urine pH fluctuates during the course of a 24 hour period. It tends to increase during the day and to decrease during the night[65,66]. Subjects can be classified with respect to their urine pH based on whether their urine during the day is mostly alkaline, acidic or with alkaline/acidic fluctuations[65]. In some subjects these patterns change from day-to-day (Alguacil et al. submitted).

Urinary pH measurement

There are several options to measure urine pH. The pH meter is used as the gold standard[67]. While some reliable digital portable models are now available, pH meters must be calibrated regularly, and they are more expensive than pH strips (also known as 'pH paper_ or 'pH dip strips). The accuracy of pH strips for urine pH measurements compared to the pH meter has been assessed in studies on animals and humans with varied results[68-71]. There have also been some attempts to estimate urine pH levels based on several factors that can influence its value: diet composition, body surface area, acute water load and exercise (lactic metabolism)[61,63,64]. As said before, Remer and Manz estimated the dietary acid load for a number of food items accounting for intestinal absorption rates of individual nutrients, and combined that information with BMI to estimate urine pH[61]. However, the estimation approach only yields an average point estimate of the urine pH for a given individual, and does not provide information on pH fluctuation patterns.

Murayama *et al* have identified three major patterns of urinary pH fluctuation during a 24-hour period according to pH= 6.0 as baseline: acidic when all readings are below 6.0, alkaline when all readings are above 6.0, and wide fluctuation below than and above than 6.0[65]. However, little is known about whether urinary pH patterns from a given 24-hour period stay constant over time. Clinicians and researchers relying in single spot AM urine samples or even samples representative from 24-hour collections may not accurately classify subjects with respect to day-to-day fluctuation of urinary pH. Alguacil et al estimated the minimum number of urine pH measurements using pH strips needed to identify subjects with

‘‘constantly acidic urine pH’’, defined as having urine pH ≤ 6.0 in two daily pH measurements early in the morning and in the evening over a week period.

Over time, ingestion of a high dietary acid load can progress to a chronic low-grade level of metabolic acidosis. The incidence of low-grade acidosis resulting from our modern diet has been well documented[58,60,72]. A chronic acidic load can cause a number of health conditions such as osteoporosis, kidney disease, and muscle wasting[58]. Sebastian et al articulates this cause and effect relationship eloquently: “Increasing evidence . . . suggests that such persisting, albeit low-grade, acidosis, and the relentless operation of responding homeostatic mechanisms, result in numerous injurious effects on the body including dissolution to bone, muscle wasting, kidney stone formation, and damage to the kidney”[58].

URINARY ALKALINIZATION

The concept of acid-alkaline balance in the field of medicine is not entirely novel, as it has been embraced by several groups within the medical community. Naturopathic medicine has used the acid-alkaline balance as a theoretical model to explain the foundation of many diseases. Allopathic medicine has examined pH modulation in specific organ systems such as the kidney to control the formation of stones and the elimination of toxins. For example, urine alkalinization has been part of the medical protocol for the management and prevention of uric acid stones[73,74].

Another aspect of the acid-alkaline balance is its role in detoxification, via either the acute removal of a drug or poison due to overdose or a nutritional protocol to support metabolic detoxification and decrease dietary toxins. Urinary pH alkalinization is a method employed under acute medical settings for the enhanced elimination of toxins in the event of a severe overdose. Conversely, acidification of urine also increases the elimination of specific toxins, although to a seemingly lesser degree[75,76]. The method by which urine alkalinization works to enhance toxin elimination is by the medically recognized process of “ion trapping,” which is the ability to enhance urinary excretion of weak acids in alkaline urine, preventing the

reabsorption of xenobiotics by renal tubules[77,78]. Proudfoot et al published a position paper on urine alkalinization, approved by the American Academy of Clinical Toxicology, which describes the use of urine alkalinization to ≥7.5 via intravenous sodium bicarbonate administration for acute poisoning and toxicity[77]. In this extensive review, the effect of urine alkalinization on the excretion of various pharmaceuticals and environmental toxins is elucidated.

This report states that "urine alkalinization increases the urine elimination of chlorpropamide, 2,4-dichlorophenoxyacetic acid, difl unisal, fluoride, mecoprop, methotrexate, phenobarbital, and salicylate"[77]. The potential of urine alkalinization to enhance toxin excretion is exemplified by the work of Blank and Wolffram, wherein they modulated urine pH in pigs with 2% dietary sodium bicarbonate, changing the urine pH from 5.7 ± 0.2 to 8.3 ± 0.1, and favorably impacted the excretion of ochratoxin A, a mycotoxin, from 9.3 ± 1.9% to 22.2 ± 4.3% of the dose[79]. Also, experimental and clinical studies confirm that urine alkalinization is effective for salicylate poisoning[78,80,81]. Garrettson and Geller showed in humans that an increase in urine pH from 6.1 to 8.1 changed the renal clearance of salicylate from 0.08 ± 0.08 L/h to 1.41 ± 0.82 L/h[78].

Therefore, if the rapid removal of toxins can be achieved to a large extent with increasing urine pH 2 points on the pH scale (which corresponds to a 100-fold decrease in H+ ions), it would follow that smaller quantities of toxins may be removed on a prolonged basis if there were a subtle increase of urine pH in the alkaline direction. Due to the logarithmic pH scale, a small change in urine pH could have a disproportionately large effect on drug and xenobiotic clearance[77]. The concept of "progressive" versus rapid alkalinization of urine may be useful as an adjunct for integrative health approaches employing metabolic detoxification using specific (nutritional) protocols. Traditionally, functional medicine has addressed detoxification or the removal of harmful endo- or exogenous substances, from the aspect of upregulating hepatic phase I and phase II enzymes to enable the chemical biotransformation of toxins into water-soluble metabolites for excretion in the urine. With the added clinical procedure of

urine alkalinization, the removal of these compounds from the body is accelerated. There are many dietary agents to assist in progressive alkalinization. Foods that are high in potassium are noteworthy (Table 7). One approach to clinically implement these strategies for metabolic detoxification involves initiating the patient on an elimination diet high in whole fruits and cruciferous vegetables and low in animal protein. In addition to potassium, cruciferous vegetables contain myriad phytochemicals, such as indole-3-carbinol and sulforaphane, which are essential for facilitating toxin biotransformation[82,83]. Additionally, these vegetables can favorably alkalize urine pH. In a pilot trial with 5 volunteers, we found that a 200 g serving of cooked broccoli, carrots, and cauliflower (with broccoli as the predominant vegetable) resulted in an increase in urine alkalinization for up to 4 hours afterwards (baseline pH = 6.20 ± 0.51; after vegetables = 6.91 ± 0.45, *P*=.01). Thus, the simple instruction to alter diet to include cruciferous vegetables can promote detoxification by up regulating phase II enzymes and by alkalizing urine, resulting in enhanced excretion of toxins.

Table 7: Potassium Content of Selected Foods (Source: http://lpi.oregonstate.edu/infocenter/minerals/potassium/)

Food	Serving	Potassium (mg)
Banana	1 medium	422
Potato, baked with skin	1 medium	926
Prune juice	6 fluid ounces	528
Plums, dried (prunes)	1/2 cup	637
Orange juice	6 fluid ounces	372
Orange	1 medium	237
Tomato juice	6 fluid ounces	417
Tomato	1 medium	292
Raisins	1/2 cup	598
Raisin bran cereal	1 cup	362
Artichoke, cooked	1 medium	343
Lima beans, cooked	1/2 cup	485
Acorn squash, cooked	1/2 cup (cubes)	448
Spinach, cooked	1/2 cup	420
Sunflower seeds	1 ounce	241
Almonds	1 ounce	200
Molasses	1 tablespoon	293

Moreover, alkalinization during metabolic detoxification may be particularly useful, as it is believed that cellular pH and the blood buffering system shift to the acid side of ideal pH reserve during detoxification due to increased circulation of xenobiotics and organic acids (eg, glucuronic acid). Furthermore, organic cation transporters that are responsible for the transport of xenobiotics in and out of the cell are pH-sensitive[84,85].

Alkalizing agents

In addition to dietary changes, nutritional supplementation for a short-term course of 3 to 4 weeks with select botanicals can facilitate metabolic detoxification. It would be appropriate to include specific alkalizing agents, such as potassium, within this nutritional regimen (Table 7). Unfortunately, the mainstream Western diet is poor in potassium, as it often lacks sufficient fruits and vegetables. The adequate intake (AI) established by the Food and Nutrition Board of the Institute of Medicine for potassium is 4.7 g daily, which is the same amount that is encouraged by the Dietary Approaches to Stop Hypertension (DASH) diet to maintain lower blood pressure levels, decrease the effects of salt intake, decrease the risk of kidney stones, and possibly reduce the incidence of bone loss. Current median intakes of potassium in the United States are roughly 35% and 50% below the AI for men and women, respectively. African Americans would particularly benefit from increased potassium intakes due to their relatively low potassium intakes and high prevalence of elevated blood pressure and salt sensitivity. For the healthy population, intake of potassium at levels higher than the AI is not of particular high risk due to the ability of the kidney to excrete excess amounts. However, potassium intakes should be closely monitored for patients with acute or chronic renal failure and pre-existing heart disease and for those on medications that increase potassium reserves in the body, such as potassium sparing medications.

Various potassium salts are available to alter urine pH. Studies using sodium bicarbonate administration reveal little effect on urinary calcium excretion in contrast to studies that used potassium bicarbonate or potassium citrate supplementation and found significant

reductions[86,87]. Potassium citrate, a therapeutic regimen to prevent kidney stones, can effectively alkalize urine. Doses of 4 to 8 g daily for 2 weeks in patients with homozygous cystinuria have effectively alkalized urine[88]. Additionally, there are a number of studies on the use of potassium citrate to counteract bone resorption caused by chronic acidemia of protein-rich diets[89-91].

The effects of potassium depend on its accompanying anion. Potassium chloride, commonly used in processed food products, does not appear to have the same alkalizing ability as potassium citrate. In a recent study, Jehle et al demonstrated that potassium citrate was more efficacious than potassium chloride in increasing bone mineral density in postmenopausal women with osteopenia[92]. Furthermore, potassium chloride led to decreased bone mineral density in the lumbar spine. Potassium citrate supplementation in these subjects resulted in a sustained and significant reduction in urinary calcium excretion and an increase in urinary citrate excretion, indicating that alkalinization had occurred[92,93].

Additionally, the citrate anion may be especially relevant for detoxification since it is an intermediate of the Krebs cycle and can potentially play a role in energy production. As many clinicians acknowledge from their experience, lack of energy is a common side effect of the first stages of metabolic detoxification.

Therefore, eating foods that are high in citrate, such as certain fruits and vegetables, may be beneficial. It is also worth noting that citrate is metabolized to bicarbonate in the body, thereby further adding to the buffering potential.

URINARY pH AS A RISK FACTOR FOR DISEASE

Urinary pH and osteoporosis

Osteoporosis is a skeletal disease that is characterized by compromised bone strength predisposing a person to an increased risk of fracture[94]. Bone strength is a combination of bone density and bone quality. Overall bone strength is difficult to measure in

the clinical setting. In the absence of fragility fracture, bone mineral density (BMD), a proxy measure that accounts for up to 70% of bone strength, is the clinical tool used to diagnose osteoporosis according to the classification of the WHO. BMD that is 2.5 standard deviations or more below the mean BMD of a young adult reference population, which is a *T*-score of −2.5 or less, qualifies for a diagnosis of osteoporosis[95]. As BMD decreases, fracture risk increases[96]. Fractures associated with osteoporosis are a major cause of morbidity, disability, mortality, and costs[97]. Mortality rate is increased by 20% in the year following a hip fracture[98]. Furthermore, 50% of women who suffer from a hip fracture will not return to their usual level of functioning and will depend on others for their daily activities; 20% of them will require long-term care[98]. Therefore, it is crucial to prevent osteoporosis and fractures.

Osteoporosis is a disease that causes pain, disability, reduced quality of life[99], mortality[100], and places substantial demands on health care budgets[101,102]. According to the acid-ash hypothesis, the modern diet produces residual acid after metabolism[59,103,104]. This diet-derived acid is thought to be buffered by bicarbonate from bone, followed by bone calcium excretion in the urine[59,103,104].

In order to maintain acid-alkaline balance throughout the various body systems, one system may be required to support another. For example, the bone matrix contains a substantial alkaline reserve such as calcium and magnesium cations that are released from the bone to balance an overly acidic dietary load in the event of inadequate buffering capacity in the blood. However, repeated borrowing of the body's alkaline reserve in response to a consistent increased (dietary) acid load can be potentially detrimental. In humans, hypercalciuria and negative calcium balance due to calcium efflux from bone may lead to metabolic bone disease and calcium nephrolithiasis[59,105,106]. In the chapter titled "Potassium" of its report *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate,* the Institute of Medicine Food and Nutrition Board states the following:

"In the setting of an inadequate intake of bicarbonate precursors, buffers in the bone matrix neutralize the excess diet-derived acid, and in the process, bone becomes demineralized. Excess diet-derived acid titrates bone and leads to increased urinary calcium and reduced urinary citrate excretion. The resultant adverse clinical consequences are possibly increased bone demineralization and increased risk of calcium containing kidney stones".

Conversely, dietary modification can positively influence bone metabolism. A diet favoring neutralization of net endogenous acid production increases calcium and phosphate retention, reduces bone resorption markers, and increases markers of bone formation in postmenopausal women[104]. Furthermore, studies have demonstrated a positive association between a high intake of alkali-rich fruits and vegetables with preservation of bone mineral density[72,107,108].

Numerous papers in the medical literature (experimental trials[59,92,104,109-114], cross sectional studies[61,103], prospective studies[72,107,115,116], and animal models[117]) identify the potential acid load of the diet as a risk factor for osteoporosis. Well-respected textbooks and reference works[118] uphold this concept. Of public health importance, the acid-ash hypothesis is marketed to the general public as the "alkaline diet", to decrease acidity, to help the body regulate its pH, and to prevent numerous disease processes. Websites, lay literature, magazine advertisements, and direct mail marketing encourage people to measure their urine pH to assess their risk of osteoporosis as well as their general health status. Urine pH of people consuming modern diets tends to be slightly acidic, with pH of approximately 6[114,119]. When urine pH is found to be acidic, the "alkaline diet" and the purchase of products to achieve acid-base balance are advocated.

Urinary pH and kidney stones

Among urinary disorders, stone formation is of paramount importance. Kidney stones are hard, rock like substances that form in the kidneys. The most common types of kidney stones are calcium oxalate, calcium phosphate and uric acid stones. These stones form by

the precipitation of concentrated amounts of minerals/ elements (calcium, oxalate, phosphate, uric acid, etc.) found in the urine. Diet is one of several factors that can promote or inhibit kidney stone formation. Other factors include heredity, environment, weight, and fluid intake. The body uses food for energy and tissue repair. After the body uses what it needs, waste products in the bloodstream are carried to the kidneys and excreted as urine. Certain foods create wastes that may form crystals in the urinary tract. In some people, the crystals grow into stones. For people who have had a kidney stone, preventing another will be a priority. In addition to dietary changes, a person may need medicine to prevent kidney stones. Metabolic risk factors involved in the generation of kidney stones are hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, and abnormally low urinary pH. Dietary-environmental risk factors include high urinary sodium and low urine volume. Rare or less commonly encountered risk factors are high urinary cystine, and alkaline urine from an infection with urea-splitting organisms[120]. The first step in preventing kidney stones is to learn what kind of stones a person's body typically makes.

Types of kidney stones

• Calcium oxalate stones are the most common. They tend to form when the urine is acidic, meaning it has a low pH. Some of the oxalate in urine is produced by the body. Calcium and oxalate in the diet play a part but are not the only factors that affect the formation of calcium oxalate stones. Dietary oxalate is an organic molecule found in many vegetables, fruits, and nuts. Calcium from bone may also play a role in kidney stone formation.

• Calcium phosphate stones are less common. Calcium phosphate stones tend to form when the urine is alkaline, meaning it has a high pH.

• Uric acid stones are more likely to form when the urine is persistently acidic, which may result from a diet rich in animal proteins and purines—substances found naturally in all food but especially in organ meats, fish, and shellfish.

• Struvite stones result from infections in the kidney. Preventing struvite stones depends on staying infection free. Diet has not been shown to affect struvite stone formation.

• Cystine stones result from a rare genetic disorder that causes cystine—an amino acid, one of the building blocks of protein—to leak through the kidneys and into the urine to form crystals.

Urinary pH plays an important role in the formation of most types of kidney stones[121]. Although struvite stones and calcium phosphate require an alkaline pH for their formation, acid uric stones, cystine stones, and to a lesser extent, calcium oxalate stones are more easily formed in acidic urine[65]. Subjects with constantly acidic pH or constantly alkaline pH on a day-to-day basis may be more likely to develop kidney stones recidives than those with fluctuant urinary pH. The identification of the type of kidney stone combined with the appropriate classification of the patients with respect to their urinary pH may enhance our understanding of the process of kidney stone formation, as well as reduce the rate of urolithiasis recurrence through improvements in treatment (including dietary counseling)[122].
Various dietary changes have been recommended to halt stone recurrence, including restricted intake of sodium, oxalate and animal proteins. Useful drugs include thiazide or indapamide to control hypercalciuria, potassium citrate to correct hypocitraturia and undue urinary acidity, and allopurinol for co-existing hyperuricemia or marked hyperuricosuria[120].

Several medications—notably acyclovir, sulfonamides, methotrexate, indinavir, and triamterene—are associated with the production of crystals that are insoluble in human urine. Intratubular precipitation of these crystals can lead to acute renal insufficiency. Many patients who require treatment with these medications have additional risk factors, such as true or effective intravascular volume depletion and underlying renal insufficiency that increase the likelihood of drug-induced intrarenal crystal deposition. Acute renal failure in this setting may be preventable if it is anticipated by appropriate drug dosing, volume expansion with high urinary flow, and alkalinization of the urine when appropriate. Renal failure may be reversible if the drug is discontinued, and by volume repletion and alkalinization of the urine when appropriate[123].

The majority of kidney stones found inside of the kidneys do not cause pain or symptoms. However, once the stones “fall out of the kidney” and enter the ureter, severe pain and blood in the urine may develop. The risk of a kidney stone “falling” out of a kidney and entering the ureter is about 50 percent over a five year period. The pain from a stone in the ureter (now a ureteral stone) occurs from the stone blocking the drainage of urine from the kidney to the bladder. This pain can be incredibly severe and is often associated with nausea and vomiting.

A variety of imaging techniques can be used to diagnosis kidney stones, but a non-contrast CT scan is the single best test available today. It is generally believed that it takes at least three months for a patient to form a kidney stone.

Once a kidney stone falls into the ureter and becomes a ureteral stone there are a variety of treatment options available. First, hopefully the patient can pass the stone on his/her own. There are some alpha-blocker medications available that have been shown to increase a patient’s chances of passing a ureteral stone. The two most common surgical procedures that may be needed to break up a stone that fails to pass are shockwave lithotripsy and ureteroscopy with laser lithotripsy. Shockwave lithotripsy (ESWL) is the administration of focused energy waves through the body onto the stone in order to break it up. Ureteroscopy with laser lithotripsy involves an urologist inserting a scope up the urinary system to the level of the stone and then using a laser to break it. Both surgeries are most commonly performed in an outpatient setting with quick recovery times. These surgeries, as well as other types of procedures, can also be used to treat kidney stones that are still in the organ, before they have a chance to fall into the ureter and cause greater problems.

Frequently with surgery to treat kidney/ureteral stones, a ureteral stent may be placed. This is a soft plastic tube that runs from the kidney, down the ureter and into the bladder. The purpose of the stent is to keep the flow of urine draining from the kidney to the bladder.

Ureteral stents are only temporary and need to be removed or exchanged after a certain amount of time.

Urinary pH and Bladder cancer

Acidic urine pH has been suggested to play an important role in human bladder carcinogenesis by influencing the urine concentration of active aromatic amines[124]. Liver-synthesized N-Glucuronides of aromatic amines like 4-aminobiphenyl, N-hydroxy-4-aminobiphenyl and N-acetylbenzidine are excreted into the urinary bladder, where they are relatively stable under neutral pH conditions[125,126]. However, in the presence of acidic conditions they are rapidly hydrolyzed leading to the formation of their corresponding arylamines, which can then undergo further metabolism to form DNA adducts[127,128].

There is also *in vitro* evidence that urine pH has a similar effect on aromatic amines derived from cigarette smoke such as 4-aminobiphenyl (4-ABP) and its metabolite *N*-hydroxy-4-aminobyphenyl (N-OH-4-ABP)[126]. For example, the half-life of 4-ABP *N*-glucuronide conjugates, before being hydrolyzed, is 11 minutes at pH 5.5 and 37 ºC compared to over 3 hours at pH 7.4[129]. Further, a toxicokinetic study showed that urine pH was a strong contributor to interindividual variation in DNA binding of ABP in the human bladder[130].

Urine pH may modify the impact of tobacco use on risk of bladder cancer in a way that is consistent with experimental data showing that acidic urine can result in cleavage of acid-labile glucuronides of carcinogenic aromatic amines[124].

A dose-response relationship in bladder cancer risk with increasing urinary acidity was observed, with no association among nonsmokers, a weak association among former smokers, a strong association among current smokers, and with evidence of interaction between having consistently acidic urinary pH and heavy smoking[131]. Since urinary pH was measured by cases after bladder cancer was diagnosed and treated, there is a concern that urinary pH may have been directly or indirectly influenced by the disease

itself[132] or its treatment, resulting in a possible spurious association.

In addition, the activity of some of the drugs used for bladder cancer treatment is pH dependant; hence, characterizing day-to-day urine pH variability might help to predict therapeutic response and toxicity in some patients[133].

2. Hypothesis

2. Hypothesis

The use of some medications can be associated with the presence or the absence of constantly acidic urine pH in humans. Some medications could influence directly the acid-base status in humans. Also, it could be possible that some medical conditions for which some medications are prescribed can influence the acid-base status.

3. Objective

3. Objective

To examine the association between subjects' medication use after hospital discharge and having constantly acidic urine pH

4. Material and methods

4. Materials and methods

Study design and data collection

Data collection for this research has been taken from a case-control study on bladder cancer. To increase internal and external validity, we have limited subject inclusion and statistical analyses for this report to the control subjects of the case-control study. In this study, 1219 incident transitional cell carcinoma (TCC) cases (84% of 1453 contacted cases) and 1271 hospital controls (88% of 1442 controls) were recruited between June 1998 and June 2001 in 18 hospitals in the following regions in Spain: Barcelona, Vallès/Bages, Asturias, Alicante, and Tenerife. Subjects were 21 to 80 years old at the time of diagnosis and resided in the catchment areas of the 18 participating hospitals. Out of the 611 control subjects with available valid pH measurements, 598 (97.87%) subjects reported information on vitamins and medications use, and after excluding two subjects with low quality of the interview, and 175 subjects with missing information in the potential cofounders (vegetable intake (n=18), fruit intake (n=15), meat intake (n=89), height (n=85), and weight (n=70), (one subject can have missing information in more than one variable)) we ended with 423 subjects, which is the base population used for this report. The study was approved by the National Cancer Institute Institutional Review Board, as well as by the ethics committees of all participating hospitals.

Data collection

All subjects were interviewed in the hospital using a computer-assisted personal interview. Before the interview, written informed consent to participate in the study was obtained from each subject. The questionnaire was designed to elicit detailed information on smoking habits, dietary factors, fluid intake, medical conditions (infections bladder/kidney stones, enlarged Prostate, circulatory diseases, heart problems, asthma, ulcers, diabetes,

osteoporosis, leukemia, cancer, benign tumors and others), occupational and residential histories, and family history of cancer.

DESCRIPTION OF THE POPULATION

The distribution of selected socio-demographic variables, age, height, weight, current BMI and daily urinary frequency in the study population and cigarette smoking is shown in Table 8. There were more men (90.3%) than women (9.7%), most of control group subjects were included in primary or less than primary education level (82.5%) and they were more likely to be living with a spouse (82.5%).

Table 8: Socio-demographic and cigarette smoking classification among controls

	N	Percent	Mean	SD
Gender				
Male	382	90.3		
Female	41	9.7		
Age at Interview	423		62.12	10.07
Height in Meters	423		1.69	0.08
Usual Weight in Kilograms	416		71.47	10.47
BMI (current)	423		27.02	3.92
Daily urinary frequency	413		6.92	2.56
Hospital region				
Barcelona (Mar/Ruti)	78	18.4		
Sabadell	44	10.4		
Alicante	42	9.9		
Tenerife	73	17.3		
Asturias	186	44.0		
Marital status				
Single	32	7.6		
Married	349	82.5		
Widowed	26	6.1		
Divorced	16	3.8		
Recategorized education levels				
Less than primary	156	36.9		
Primary	193	45.6		
Secondary and higher	69	16.3		
Other	5	1.2		
Cigarette smoking				
Non-smokers	149	35.3		
Former smokers	191	45.3		
Current smokers	82	19.4		
Missing	1	0.2		

Subjects were selected from patients admitted to the same hospital around the same time as their matched bladder cancer cases for diseases/conditions (Table 9) unrelated to smoking (36% hernias, 15% urology, 28% traumatology/orthopedics, 7% abdominal obstruction, 1% burns, 11% minor/major surgery and 2% ophthalmology).

Table 9. Diagnostic groups among controls during hospitalization

Diseases/Conditions	n	Percent
Urology	62	14.7
Surgical Traumatology	24	5.7
Orthopedics Prosthesis	3	0.7
Traumatology	15	3.5
Ophthalmology	9	2,1
Minor Surgery	4	0.9
Major Surgery	43	10.2
Hernia	151	35.7
Fracture	78	18.4
Burn	4	0.9
Abdominal obstruction	30	7.1

Urine pH Measurement

Study participants were trained to test their urine pH with dipsticks at home and record results into a diary. 611 (48.1%) control subjects (free of cancer) returned diaries with complete data on urine pH, which they measured twice a day (first void in the morning and early in the evening) during 4 consecutive days two weeks after hospital discharge.

Study participants were also asked to list on the pH diary all medications and vitamins taken during each of the four days of pH measurements. All medications listed were tabulated and coded according to the Anatomical Therapeutic Chemical (ATC) classification.

Subjects who returned a complete urine diary were similar to those who did not with regard to grams of fruits and vegetables intake, BMI, and smoking status. Subjects with all of their pH readings less than or equal to 6.0 were categorized as having a consistently acidic urine pH. As urinary pH reflects several factors that can vary over time, we adopted this conservative definition to maximize the probability that such individuals would have had a long-term tendency to have acidic urine.

Coding of medications

Drugs can be classified in different ways according to their mode of action, their indications, or their chemical structure.

Each classification system will have its advantages and limitations and its usefulness will depend on the purpose, the setting used and the user's knowledge of the methodology.

Comparisons between countries may require a classification system different from that needed for a local comparison (e.g. between different wards in a hospital). Of the various systems proposed over the years, only two have survived to attain a dominant position in drug utilization research worldwide. These are the «Anatomical Therapeutic» (AT) classification developed by the European Pharmaceutical Market Research Association (EPhMRA) and the «Anatomical Therapeutic Chemical» (ATC) classification developed by Norwegian researchers.

ATC CLASSIFICATION

We coded the medications reported in the urine pH diary using the Anatomical Therapeutic Chemical (ATC) classification system, where the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs were classified in groups at five different levels. Drugs are classified in groups at five different levels. The drugs are divided into fourteen main groups (1st level), with pharmacological/therapeutic subgroups (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level

is the chemical substance (active ingredient). The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups.

The main purpose of the ATC classification is as a tool for presenting drug utilization statistics and it is recommended by WHO (Collaborating Centre for International Drug Monitoring in Uppsala, Sweden) for use in international comparisons. The ATC classification is also the basis for the classification of adverse drug reactions used by the WHO.

Nomenclature from International nonproprietary names (INN) is preferred. If INN names are not assigned, USAN (United States Adopted Name) or BAN (British Approved Name) names are usually chosen and WHO's list of drug terms (Pharmacological action and therapeutic use of drugs - List of Terms) is used when naming the different ATC levels.

Medicinal products are classified according to the main therapeutic use of their main active ingredient, on the basic principle of assigning only one ATC code for each pharmaceutical formulation (i.e. similar ingredients, strength and pharmaceutical form).

A medicinal product can be given more than one ATC code if it is available in two or more strengths or formulations with clearly different therapeutic uses, and different pharmaceutical forms for topical and systemic use are also given separate ATC codes.

The ATC system is not strictly a therapeutic classification system. At all ATC levels, ATC codes can be assigned according to the pharmacological properties of the product. Subdivision on the basis of mechanism of action will understandably be rather broad, since a very detailed classification of this kind would result in having only one substance per subgroup, which is better avoided (e.g. in the case of antidepressants). Some ATC groups are subdivided into both chemical and pharmacological groups (e.g. ATC group J05A - Agents affecting the virus directly). If a new substance fits in both a chemical and pharmacological fourth level, the pharmacological group is normally chosen.

Substances classified as having the same ATC fourth level should not be considered as pharmacotherapeutically equivalent since the profiles for their mode of action, therapeutic effects, drug interactions and adverse drug reactions may differ.

As the drugs available and their uses are continuously changing and expanding, regular revisions of the ATC system are necessary. An important principle is to keep the number of alterations to a minimum. Before alterations are made, any potential difficulties arising for the users of the ATC system are considered and related to the benefits that would be achieved by the alteration.

Changes to the ATC classification would be made when the main use of a drug had clearly changed, and when new groups are required to accommodate new substances or to improve the specificity of the groupings.

Because the ATC system separates drugs into groups at five levels (described above), statistics on drug utilization grouped at the five different levels can be provided. The information available ranges from figures showing total use of all drug products classified e.g. in main group C - Cardiovascular system (first level), to figures for the different subgroups (i.e. second, third and fourth level) to figures for the use of the separate substances.
More detailed information can be obtained at the lower (i.e. the fourth and fifth) levels. The higher levels are used if comparison of drug groups is the aim of a study (see Fig. 5). This gives a better overview and trends in drug use related to different therapeutic areas can easily be identified.

It has to be taken into account that all international standards demand compromises and a drug classification system is no exception to this rule. Drugs may be used for two or more equally important indications, and the main therapeutic use of a drug may differ from one country to another. This will often result in several possible alternatives for classification, and a decision has to be made regarding the main use.

Statistical Analysis

To estimate the effects of medication on urinary pH, we calculated odds ratios (OR) and 95% confidence intervals (95% CI) using unconditional logistic regression, with two strategies: a) Fixed terms entered for all potential confounding variables (i.e., age at interview, sex, study region, vegetable intake, fruit intake, meat intake, height, weight, and vitamin C use) plus the medication of interest, building one model for each medication at the segregation levels of 1, 3, 4, 5, and 7 digits of the ATC classification; and b) fixed terms strategy (for all potential confounding factors) combined with step wise strategy entering all medications from a given segregation level of the ATC Classification with a p value for entering variables=0.15, and a p value for excluding variables from the model=0.2.

5. Results

5. RESULTS

Relationship between pH and confounding variables

The association between urinary pH and confounding factors that could potentially influence urine pH, including diet composition (daily meat intake, vegetable intake, fruit intake, and/or combined vegetable/fruit intake), gender, age, body surface area, cigarette smoking status, alcohol consumption, urinary frequency, NSAIDs consumption, study region, finished studies, marital status or season for pH measurement are shown on Table 10. Sex, cigarette smoking status, alcohol consumption, urinary frequency, NSAIDs consumption, usual BMI, grams of meat intake, and grams of vegetables intake were not significantly associated to influence on having or not having consistently acidic urine pH. Age, study region, finished studies, season for pH measurement, grams of fruits and grams of vegetables/fruit intake were significantly associated to influence on having or not having a constant acidification of urine among controls (Table 10).

Table 10: Influence of various factors on urine pH among controls

	Maximum urine pH		
	>6	≤6	p
Female gender	60.9%	39.1%	0.991
Age mean	63.5	61.6	0.061
Study region			
Barcelona	59.0%	41.0%	
Sabadell	60.3%	39.7%	
Alicante	60.4%	39.6%	
Tenerife	76.0%	24.0%	
Asturias	56.1%	43.9%	0.012
Marital status			
Single	51.4%	48.6%	
Married	60.5%	39.5%	
Widowed	54.5%	45.5%	
Divorced	77.3%	22.7%	0.345
Finished education			
Less than primary	70.4%	29.6%	
Primary	55.2%	44.8%	
Secondary and higher	53.8%	46.2%	
Other	62.5%	37.5%	0.002
Cigarette smoking			
Ever	61.4%	38.6%	
Former	62.6%	37.4%	
Current	55.4%	44.6%	0.413

Table 10 (Cont'd): Influence of various factors on urine pH among controls

	Maximum urine pH		
	>6	≤6	p
Season for pH measurement			
Summer	51.8%	48.2%	
Fall	66.1%	33.9%	
Winter	66.7%	33.3%	
Spring	59.8%	40.2%	0.048
Alcohol (grs/day)	36.1	31.35	0.61
Fluids (mL/day)	2006	2192	0.43
Maximum urinary frequency			
9+	58.9%	41.1%	
6-9	60.1%	39.9%	
<6	63.5%	36.5%	0.709
N SAIDS			
Never	90.9%	93.9%	
Regular	3.6%	2.8%	
Non-regular	5.5%	4.65%	0.89
Heart Attack	47.4%	52.6%	0.093
BMI (usual)			
24.2	62.0%	38.0%	
24.3-26.9	61.2%	38.8%	
27-29.4	55.8%	44.2%	
>29.4	67.6%	32.4%	0.435
Meat (grs/day)	120.6	119.6	0.99
Vegetables/fruits (grs/day)	806.3	610.4	0.001
Vegetables (grs/day)	296.8	246.7	0.13
Fruits (grs/day)	509.0	363.2	<0.001

Association between medications and urine pH. Magnitude of the association estimated by logistic regression. Fixed terms models

In our study population, 163 subjects (38.5%) had acidic urine and 260 (61.5%) had not acid urine pH values. The association (using logistic regression models) between medication use after hospital discharge and having constantly acidic urine pH values are shown in the Tables below (Tables 11 to 27).

Table 11: Association between urine pH and stomatological preparations, and drugs for acid related disorders. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
ALIMENTARY TRACT AND METABOLISM (A)	29	17.79	44	16.92	1.13	(0.66 - 1.94)
STOMATOLOGICAL PREPARATIONS (A01)	0	0	7	2.69	0.10	(0.01 - 1.82)
STOMATOLOGICAL PREPARATIONS (A01A)	0	0	7	2.69	0.10	(0.01 - 1.82)
(A01AE01)	0	0	7	2.69	0.10	(0.01 - 1.82)
DRUGS FOR ACID RELATED DISORDERS (A02)	17	10.43	26	10	1.11	(0.57 - 2.18)
ANTACIDS (A02A)	1	0.61	6	2.31	0.33	(0.04 - 2.96)
Combinations and complexes of aluminium, calcium and magnesium compounds (A02AD)	1	0.61	3	1.15	0.67	(0.06 - 7.24)
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE - GORD (A02B)	16	9.82	24	9.23	1.09	(0.55 - 2.18)
H2-receptor antagonists (A02BA)	7	4.29	13	5	0.90	(0.33 - 2.42)
Ranitidine (A02BA02)	6	3.68	12	4.62	0.83	(0.30 - 2.35)
Proton pump inhibitors (A02BC)	8	4.91	10	3.85	1.21	(0.46 - 3.18)
Omeprazole (A02BC01)	6	3.68	5	1.92	1.67	(0.49 - 5.71)
Lansoprazole (A02BC03)	0	0	3	1.15	0.23	(0.01 - 4.38)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 12: Association between urine pH and drugs for functional gastrointestinal disorders, constipation, digestives and diabetes. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS (A03)	3	1.84	3	1.15	1.59	(0.30 - 8.30)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS (A03A)	1	0.61	2	0.77	0.74	(0.06 - 8.51)
DRUGS FOR CONSTIPATION (A06)	3	1.84	3	1.15	1.61	(0.32 - 8.21)
DRUGS FOR CONSTIPATION (A06A)	3	1.84	3	1.15	1.61	(0.32 - 8.21)
DIGESTIVES, INCL. ENZYMES (A09)	2	1.23	1	0.38	4.40	(0.38 - 50.65)
DIGESTIVES, INCL. ENZYMES (A09A)	2	1.23	1	0.38	4.40	(0.38 - 50.65)
DRUGS USED IN DIABETES (A10)	5	3.07	11	4.23	0.74	(0.24 - 2.24)
INSULINS AND ANALOGUES (A10A)	0	0	7	2.69	0.10	(0.01 - 1.82)
BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS (A10B)	5	3.07	5	1.92	1.58	(0.43 - 5.81)
Sulfonamides, urea derivatives (A10BB)	4	2.45	4	1.54	1.54	(0.36 - 6.64)
Glibenclamide (A10BB01)	2	1.23	3	1.15	0.92	(0.15 - 5.81)
Alpha glucosidase inhibitors (A10BF)	1	0.61	1	0.38	1.76	(0.10 - 30.23)
Acarbose (A10BF01)	1	0.61	1	0.38	1.76	(0.10 - 30.23)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 13: Association between urine pH and Vitamins, and mineral supplements. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
VITAMINS (A11)	4	2.45	5	1.92	1.47	(0.38 - 5.74)
ASCORBIC ACID (VITAMIN C), INCL. COMBINATIONS (A11G)	1	0.61	3	1.15	0.58	(0.06 - 5.76)
Ascorbic acid (vit C) (A11GA01)	1	0.61	3	1.15	0.58	(0.06 - 5.76)
OTHER PLAIN VITAMIN PREPARATIONS (A11H)	3	1.84	1	0.38	6.30	(0.60 - 66.41)
Nicotinamide (A11HA02)	2	1.23	1	0.38	4.45	(0.35 - 55.82)
MINERAL SUPPLEMENTS (A12)	0	0	7	2.69	0.10	(0.01 - 1.82)
CALCIUM (A12A)	0	0	4	1.54	0.17	(0.01 - 3.26)
Calcium carbonate (A12AA04)	0	0	4	1.54	0.17	(0.01 - 3.26)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 14: Association between urine pH and antithrombotic agents, and antianemic preparations. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
BLOOD AND BLOOD FORMING ORGANS (B)	16	9.82	29	11.15	0.86	(0.44 - 1.66)
ANTITHROMBOTIC AGENTS (B01)	14	8.59	24	9.23	0.89	(0.44 - 1.81)
ANTITHROMBOTIC AGENTS (B01A)	14	8.59	24	9.23	0.89	(0.44 - 1.81)
Vitamin K antagonists (B01AA)	3	1.84	3	1.15	2.55	(0.47 - 13.94)
Acenocoumarol (B01AA07)	3	1.84	3	1.15	2.55	(0.47 - 13.94)
Heparin group (B01AB)	2	1.23	11	4.23	0.27	(0.06 - 1.25)
Enoxaparin (B01AB05)	2	1.23	5	1.92	0.63	(0.12 - 3.44)
Platelet aggregation inhibitors excl. Heparin (B01AC)	8	4.91	8	3.08	1.43	(0.51 - 4.07)
Ticlopidine (B01AC05)	3	1.84	2	0.77	1.95	(0.32 - 12.07)
Triflusal (B01AC18)	3	1.84	5	1.92	0.82	(0.18 - 3.80)
ANTIANEMIC PREPARATIONS (B03)	2	1.23	2	0.77	1.92	(0.26 - 13.99)
IRON PREPARATIONS (B03A)	1	0.61	1	0.38	2.12	(0.13 - 34.99)
Iron bivalent, oral preparations (B03AA)	0	0	1	0.38	0.53	(0.02 - 13.06)
VITAMIN B12 AND FOLIC ACID (B03B)	2	1.23	0	0	6.45	(0.29 - 144.00)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 15: Association between urine pH and Cardiac Glycosides, vasodilators used in cardiac diseases, and antihypertensives. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
CARDIOVASCULAR SYSTEM (C)	42	25.77	68	26,15	1,04	(0,64 - 1,68)
CARDIAC THERAPY (C01)	11	6.75	11	4,23	1,64	(0,68 - 3,97)
CARDIAC GLYCOSIDES (C01A)	7	4.29	4	1,54	3,30	(0,92 - 11,80)
Digitalis glycosides (C01AA)	3	1.84	1	0,38	6,28	(0,61 - 64,12)
Acetyldigoxin (C01AA02)	1	0.61	3	1,15	0,75	(0,07 - 7,51)
Digoxin (C01AA05)	3	1.84	1	0,38	6,28	(0,61 - 64,12)
ANTIARRHYTHMICS, CLASS I AND III (C01B)	0	0	1	0,38	0,53	(0,02 - 13,06)
VASODILATORS USED IN CARDIAC DISEASES (C01D)	5	3.07	6	2,31	1,19	(0,35 - 4,05)
Organic nitrates (C01DA)	5	3.07	6	2,31	1,19	(0,35 - 4,05)
Glyceryl trinitrate (C01DA02)	3	1.84	1	0,38	5,09	(0,51 - 50,84)
Isosorbide mononitrate (C01DA14)	2	1.23	3	1,15	0,88	(0,14 - 5,46)
ANTIHYPERTENSIVES (C02)	3	1.84	7	2,69	0,65	(0,15 - 2,80)
Antiadrenergic agents, peripherally acting (C02C)	3	1.84	7	2,69	0,65	(0,15 - 2,80)
Alpha-adrenoreceptor antagonists (C02CA)	3	1.84	7	2,69	0,65	(0,15 - 2,80)
Doxazosin (C02CA04)	2	1.23	7	2,69	0,39	(0,07 - 2,15)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 16: Association between urine pH and diuretics. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
DIURETICS (C03)	13	7.98	23	8,85	0,88	(0,42 - 1,85)
LOW-CEILING DIURETICS, THIAZIDES (C03A)	7	4.29	10	3,85	1,05	(0,38 - 2,94)
Hydrochlorothiazide (C03AA03)	7	4.29	9	3,46	1,17	(0,41 - 3,35)
LOW-CEILING DIURETICS, EXCL. THIAZIDES (C03B)	2	1.23	4	1,54	0,83	(0,14 - 4,80)
Sulfonamides, plain (C03BA)	2	1.23	4	1,54	0,83	(0,14 - 4,80)
Indapamide (C03BA11)	2	1.23	2	0,77	2,04	(0,27 - 15,73)
HIGH-CEILING DIURETICS (C03C)	4	2.45	7	2,69	1,02	(0,28 - 3,71)
Sulfonamides, plain (C03CA)	4	2.45	5	1,92	1,50	(0,37 - 6,01)
Furosemide (C03CA01)	3	1.84	4	1,54	1,47	(0,30 - 7,25)
Torasemide (C03CA04)	1	0.61	3	1,15	0,54	(0,06 - 5,31)
POTASSIUM-SPARING AGENTS (C03D)	3	1.84	6	2,31	0,57	(0,13 - 2,45)
Amiloride (C03DB01)	3	1.84	2	0,77	1,65	(0,25 - 10,85)
DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION (C03E)	3	1.84	5	1,92	0,70	(0,15 - 3,21)
Low-ceiling diuretics and potassium-sparing agents (C03EA)	3	1.84	3	1,15	1,10	(0,20 - 5,96)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 17: Association between urine pH and peripheral vasodilators, vasoprotectives, and beta blocking agents. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
PERIPHERAL VASODILATORS (C04)	4	2.45	4	1.54	1.43	(0.32 - 6.46)
PERIPHERAL VASODILATORS (C04A)	4	2.45	4	1.54	1.43	(0.32 - 6.46)
Purine derivatives (C04AD)	4	2.45	3	1.15	1.80	(0.36 - 9.00)
Pentoxifylline (C04AD03)	4	2.45	3	1.15	1.80	(0.36 - 9.00)
VASOPROTECTIVES (C05)	1	0.61	5	1.92	0.40	(0.05 - 3.56)
CAPILLARY STABILIZING AGENTS (C05C)	1	0.61	4	1.54	0.46	(0.05 - 4.20)
BETA BLOCKING AGENTS (C07)	11	6.75	12	4.62	1.73	(0.72 - 4.15)
BETA BLOCKING AGENTS (C07A)	11	6.75	12	4.62	1.73	(0.72 - 4.15)
Beta blocking agents, selective (C07AB)	8	4.91	9	3.46	1.59	(0.58 - 4.39)
Atenolol (C07AB03)	5	3.07	4	1.54	2.04	(0.52 - 7.98)
Bisoprolol (C07AB07)	2	1.23	6	2.31	0.65	(0.12 - 3.47)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 18: Association between urine pH and calcium channel blockers. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
CALCIUM CHANNEL BLOCKERS (C08)	12	7.36	21	8.08	0.86	(0.40 - 1.85)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS (C08C)	4	2.45	13	5	0.43	(0.13 - 1.39)
Dihydropyridine derivatives (C08CA)	4	2.45	13	5	0.43	(0.13 - 1.39)
Amlodipine (C08CA01)	1	0.61	3	1.15	0.51	(0.05 - 5.23)
Nifedipine (C08CA05)	1	0.61	5	1.92	0.30	(0.03 - 2.59)
Nimodipine (C08CA06)	2	1.23	2	0.77	1.12	(0.14 - 8.94)
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS (C08D)	8	4.91	8	3.08	1.62	(0.59 - 4.46)
Verapamil (C08DA01)	4	2.45	2	0.77	2.94	(0.52 - 16.69)
Benzothiazepine derivatives (C08DB)	4	2.45	6	2.31	1.13	(0.31 - 4.12)
Diltiazem (C08DB01)	4	2.45	6	2.31	1.13	(0.31 - 4.12)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 19: Association between urine pH and agents acting on the Renin-Angiotensin system, and lipid modifying agents. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM (C09)	14	8.59	28	10.77	0.78	(0,39 - 1,56)
ACE INHIBITORS, PLAIN (C09A)	13	7.98	26	10	0.76	(0.37 - 1.56)
ACE inhibitors, plain (C09AA)	8	4.91	19	7.31	0.62	(0.26 - 1.49)
Captopril (C09AA01)	1	0.61	5	1.92	0.28	(0.03 - 2.47)
Enalapril (C09AA02)	6	3.68	10	3.85	1.07	(0.37 - 3.09)
ACE INHIBITORS, COMBINATIONS (C09B)	5	3.07	7	2.69	1.18	(0.36 - 3.87)
ACE inhibitors and diuretics (C09BA)	2	1.23	7	2.69	0.48	(0.10 - 2.41)
ANGIOTENSIN II ANTAGONISTS, PLAIN (C09C)	1	0.61	2	0.77	1.12	(0.09 - 13.42)
Angiotensin II antagonists, plain (C09CA)	1	0.61	2	0.77	1.12	(0.09 - 13.42)
LIPID MODIFYING AGENTS (C10)	11	6.75	16	6.15	1.23	(0.54 - 2.78)
LIPID MODIFYING AGENTS, PLAIN (C10A)	11	6.75	16	6.15	1.23	(0.54 - 2.78)
HMG CoA reductase inhibitors (C10AA)	8	4.91	14	5.38	1.08	(0.43 - 2.72)
Simvastatin (C10AA01)	1	0.61	3	1.15	0.55	(0.06 - 5.36)
Atorvastatin (C10AA05)	3	1.84	3	1.15	2.53	(0.46 - 13.82)
Fibrates(C10AB)	4	2.45	2	0.77	2.58	(0.45 - 14.63)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 20: Association between urine pH and urologicals. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
GENITO URINARY SYSTEM AND SEX HORMONES (G)	12	7.36	13	5	1.40	(0.58 - 3.37)
UROLOGICALS (G04)	10	6.13	13	5	1.14	(0.46 - 2.84)
UROLOGICALS (G04B)	0	0	1	0.38	0.53	(0.02 - 13.06)
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY (G04C)	10	6.13	13	5	1.14	(0.46 - 2.84)
Alpha-adrenoreceptor antagonists (G04CA)	6	3.68	7	2.69	1.24	(0.39 - 3.97)
Tamsulosin (G04CA02)	4	2.45	5	1.92	1.03	(0.25 - 4.24)
Terazosin (G04CA03)	1	0.61	1	0.38	1.58	(0.09 - 26,52)
Testosterone-5-alpha reductase inhibitors (G04CB)	1	0.61	4	1.54	0.38	(0.04 - 3,83)
Finasteride (G04CB01)	1	0.61	4	1.54	0.38	(0.04 - 3,83)
Other drugs used in benign prostatic hypertrophy (G04CX)	3	1.84	3	1.15	1.58	(0.29 - 8,56)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 21: Association between urine pH and systemic hormonal preparations. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS (H)	2	1.23	10	3.85	0.37	(0.08 - 1.75)
CORTICOSTEROIDS FOR SYSTEMIC USE (H02)	1	0.61	6	2.31	0.29	(0.03 - 2.55)
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN (H02A)	1	0.61	6	2.31	0.29	(0.03 - 2.55)
Glucocorticoids (H02AB)	1	0.61	3	1.15	0.54	(0.05 - 5.70)
Budesonide (H02AB16)	0	0	3	1.15	0.23	(0.01 - 4.38)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 22: Association between urine pH and antibacterials for systemic use. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
ANTIINFECTIVES FOR SYSTEMIC USE (J)	9	5.52	19	7.31	0.75	(0.32 - 1.75)
ANTIBACTERIALS FOR SYSTEMIC USE (J01)	8	4.91	18	6.92	0.68	(0.28 - 1.68)
BETA-LACTAM ANTIBACTERIALS, PENICILLINS (J01C)	3	1.84	10	3.85	0.46	(0.12 - 1.75)
Amoxicillin (J01CA04)	3	1.84	8	3.08	0.62	(0.16 - 2.43)
Amoxicillin and enzyme inhibitor (J01CR02)	1	0.61	6	2.31	0.26	(0.03 - 2.25)
QUINOLONE ANTIBACTERIALS (J01M)	3	1.84	7	2.69	0.76	(0.18 - 3.17)
Ciprofloxacin (J01MA02)	3	1.84	7	2.69	0.76	(0.18 - 3.17)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 23: Association between urine pH and drugs used in endocrine therapy and musculo-eskeletal system. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS (L)	5	3.07	5	1.92	1.35	(0.37 - 4.92)
ENDOCRINE THERAPY (L02)	2	1.23	4	1.54	0.61	(0.10 - 3.63)
HORMONE ANTAGONISTS AND RELATED AGENTS (L02B)	1	0.61	4	1.54	0.36	(0.04 - 3.29)
MUSCULO-SKELETAL SYSTEM (M)	16	9.82	22	8.46	1.33	(0.67 - 2.67)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS (M01)	10	6.13	17	6.54	1.00	(0.44 - 2.28)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS (M01A)	10	6.13	17	6.54	1.00	(0.44 - 2.28)
Acetic acid derivatives and related substances (M01AB)	5	3.07	10	3.85	0.93	(0.31 - 2.84)
Diclofenac (M01AB05)	5	3.07	8	3.08	1.12	(0.35 - 3.55)
Propionic acid derivatives (M01AE)	4	2.45	2	0.77	2.72	(0.48 - 15.61)
Ibuprofen (M01AE01)	3	1.84	2	0.77	2.02	(0.32 - 12.90)
ANTIGOUT PREPARATIONS (M04)	5	3.07	5	1.92	2.08	(0.56 - 7.73)
Uric acid production inhibitors (M04AA)	5	3.07	5	1.92	2.08	(0.56 - 7.73)
Allopurinol (M04AA01)	5	3.07	5	1.92	2.08	(0.56 - 7.73)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 24: Association between urine pH and analgesics, and antiepileptics. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
NERVOUS SYSTEM (N)	30	18.4	66	25.38	0.68	(0.41 - 1.11)
ANALGESICS (N02)	25	15.34	43	16.54	0.92	(0.54 - 1.60)
OTHER ANALGESICS AND ANTIPYRETICS (N02B)	24	14.72	40	15.38	0.97	(0.56 - 1.70)
Salicylic acid and derivatives (N02BA)	6	3.68	16	6.15	0.62	(0.24 - 1.64)
Acetylsalicylic acid (N02BA01)	7	4.29	16	6.15	0.74	(0.30 - 1.87)
Pyrazolones (N02BB)	14	8.59	14	5.38	1.62	(0.73 - 3.59)
Metamizole sodium (N02BB02)	14	8.59	14	5.38	1.62	(0.73 - 3.59)
Anilides (N02BE)	5	3.07	13	5	0.64	(0.22 - 1.87)
Paracetamol (N02BE01)	5	3.07	13	5	0.64	(0.22 - 1.87)
ANTIEPILEPTICS (N03)	3	1.84	3	1.15	2.02	(0.39 - 10.44)
ANTIEPILEPTICS (N03A)	3	1.84	3	1.15	2.02	(0.39 - 10.44)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 25: Association between urine pH and anxiolytics, hypnotics/sedatives, and antidepressants. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
PSYCHOLEPTICS (N05)	5	3.07	22	8.46	0.34	(0.12 - 0.94)
ANXIOLYTICS (N05B)	4	2.45	18	6.92	0.33	(0.11 - 1.03)
Benzodiazepine derivatives (N05BA)	4	2.45	17	6.54	0.35	(0.11 - 1.09)
Diazepam (N05BA01)	2	1.23	2	0.77	2.42	(0.32 - 18.40)
Potassium clorazepate (N05BA05)	0	0	3	1.15	0.23	(0.01 - 4.38)
Lorazepam (N05BA06)	1	0.61	5	1.92	0.30	(0.03 - 2.69)
Bromazepam (N05BA08)	0	0	4	1.54	0.17	(0.01 - 3.26)
Alprazolam (N05BA12)	1	0.61	3	1.15	0.53	(0.05 - 5.27)
HYPNOTICS AND SEDATIVES (N05C)	1	0.61	4	1.54	0.30	(0.03 - 3.24)
PSYCHOANALEPTICS (N06)	1	0.61	9	3.46	0.18	(0.02 - 1.49)
ANTIDEPRESSANTS (N06A)	1	0.61	7	2.69	0.24	(0.03 - 1.99)
Amitriptyline (N06AA09)	1	0.61	2	0.77	1.42	(0.12 - 16.71)
Selective serotonin reuptake inhibitors (N06AB)	0	0	4	1.54	0.17	(0.01 - 3.26)
Paroxetine (N06AB05)	0	0	3	1.15	0.23	(0.01 - 4.38)
PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS (N06B)	0	0	2	0.77	0.32	(0.02 - 6.63)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 26: Association between urine pH and drugs for obstructive airway diseases (inhalants), and adrenergics for systemic use. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
RESPIRATORY SYSTEM (R)	3	1.84	20	7.69	0.25	(0.07 - 0.85)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES (R03)	1	0.61	11	4.23	0.17	(0.02 - 1.34)
ADRENERGICS, INHALANTS (R03A)	1	0.61	8	3.08	0.23	(0.03 - 1.92)
Selective beta-2-adrenoreceptor agonists (R03AC)	0	0	6	2.31	0.12	(0.01 - 2.14)
Salbutamol (R03AC02)	1	0.61	3	1.15	0.54	(0.05 - 5.45)
OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS (R03B)	1	0.61	7	2.69	0.30	(0.04 - 2.48)
Glucocorticoids (R03BA)	1	0.61	7	2.69	0.30	(0.04 - 2.48)
Anticholinergics (R03BB)	1	0.61	3	1.15	0.70	(0.07 - 7.05)
Ipratropium bromide (R03BB01)	1	0.61	3	1.15	0.70	(0.07 - 7.05)
ADRENERGICS FOR SYSTEMIC USE (R03C)	1	0.61	2	0.77	0.81	(0.07 - 9.50)
Selective beta-2-adrenoreceptor agonists (R03CC)	1	0.61	2	0.77	0.81	(0.07 - 9.50)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 27: Association between urine pH and other systemic drugs for obstructive airway diseases, and cough and cold preparations. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES (R03D)	0	0	5	1.92	0.14	(0.01 - 2.59)
Xanthines (R03DA)	0	0	5	1.92	0.14	(0.01 - 2.59)
Theophylline (R03DA04)	0	0	5	1.92	0.14	(0.01 - 2.59)
COUGH AND COLD PREPARATIONS (R05)	1	0.61	7	2.69	0.21	(0.02 - 1.74)
EXPECTORANTS, EXCL. COMBINATIONS WITH COUGH SUPPRESSANTS (R05C)	0	0	1	0.38	0.53	(0.02 - 13.06)
Mucolytics (R05CB)	0	0	1	0.38	0.53	(0.02 - 13.06)
COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS (R05D)	1	0.61	6	2.31	0.26	(0.03 - 2.21)
Codeine (R05DA04)	1	0.61	5	1.92	0.33	(0.04 - 2.96)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

The association between drugs included in the major group “Vitamins, and mineral supplements” and urinary pH is shown in Tables 11-13. Some drugs acting on “alimentary tract and metabolism” showed associations close to statistical significance. In Table 11 we found that 2.7% of subjects without constantly acidic urinary pH reported taking “stomatological preparations”, founding none of them with acidic urinary pH (OR=0.10, 95%CI: 0.01 – 1.82; p=0.058). A similar situation is shown in Table 17 where 2.7% of subjects were taking drugs from the therapeutic group of “insulins and analogues” used in diabetes, and again none of them had acidic urine pH (OR=0.10, 95%CI: 0.01 – 1.82; p=0.058). Finally in this anatomical main group (“alimentary tract and metabolism”), we again found (see Table 13) that 2.7% of our study population subjects were taking “mineral supplements” (p=0.058) and none of them had acidic urine pH (OR=0.10, 95%CI: 0.01 – 1.82).

From drugs acting in the anatomical group of “blood and blood forming organs” we found that the heparin group showed an association close to statistical significance (p=0.094) in Table 14, where subjects taking these medications found to be associated with non-development of acidic urine pH (OR=0.27, 95%CI: 0.06 – 1.25).

The association between drugs acting on the cardiovascular system and urine pH are shown from Table 5 to Table 19. An association close to statistical significance was found in the pharmacological group of “cardiac glycosides” (p=0.067). Subjects taking cardiac glycosides were three times more likely to have acidic urine pH (OR=3.30, 95%CI: 0.92 – 11.80). Specifically, digoxin (see Table 15) showed a suggestion of an association with the generation of acidic urine pH levels (OR=6.28, 95%CI: 0.61 – 64.12). The medications included in the pharmacological groups of “antihypertensives, diuretics, peripheral vasodilators, vasoprotectives, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system and lipid modifying agents” did not show any association with urinary pH in our study population (all p values above 0.15) (Tables 15-19).

The results obtained for drugs acting on genito urinary system and sex hormones (urologicals) were not found to have statistically significant association values in our analysis (Table 20).

The results obtained for systemic hormonal preparations (excluding sex hormones and insulins) were not found to have statistically significant association values in our analysis (Table 21).

The results obtained for “antiinfectives for systemic use” did not reach statistically significance in our analysis (Table 22).

The results obtained for antineoplastic and immunomodulating agents (endocrine therapy) and for drugs acting in musculo-skeletal system were not statistically significant in our analysis (Table 23).

In Table 24 and 25, we observe that drugs acting on the “nervous system” had an inverse association with acidic urine pH close to statistically significance (OR=0.68, 95%CI: 0.41 – 1.11; p=0.125). Among these drugs statistically significant results were found in the group of “psycholeptics”. Psycholeptics were found to be the most representatives on giving this association to non-acidic urine development (OR=0.34, 95%CI: 0.12 – 0.94; p=0.038). Most of this psycholeptics (Table 25) taken by our study subjects were in the pharmacological group of “anxiolytics” (OR=0.33, 95%CI: 0.11 – 1.03) and more concretely most of them were benzodiazepine derivatives (OR=0.35, 95%CI: 0.11 – 1.09). Also, “psychoanaleptics” showed a suggestion of association with not development of acidic urine pH on our results (OR=0.18, 95%CI: 0.02 – 1.49, p=0.113). Finally, “analgesics and antiepileptics” were not found to have a significant influence on urine pH levels among our study population (Table 24).

Finally, the results for drugs used on the “respiratory system” were found to have statistically significant asociation in our analysis results (OR=0.25, 95%CI: 0.07 – 0.85; p=0.027). In

Table 26 and 27 we can see the suggested association with non-acidic urine pH that is given by “drugs used in obstructive airway diseases” (OR=0.17, 95%CI: 0.02 – 1.34; p=0.092), where “selective beta-2-adrenoreceptor agonists” (p=0.085) and “xanthenes”, more concretely “theophylline” (p=0.125), showed the most significant results in our analysis. Also, the use of “cold and cough preparations” showed a suggested association on the generation of non-acidic urine pH in our analysis (p=0.147).

Next are shown (Table 28) all the medications most significantly associated in our statistical analysis (p≤0.15) to influence on the generation or not generation of constantly acidic urine (summarize from the results showed in Tables 11-27).

Table 28. Influence of selected medications (p≤0.15) on urine pH. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
STOMATOLOGICAL PREPARATIONS (A01)	0	0	7	2.69	0.10	(0.01 - 1.82)
STOMATOLOGICAL PREPARATIONS (A01A)	0	0	7	2.69	0.10	(0.01 - 1.82)
(A01AE01)	0	0	7	2.69	0.10	(0.01 - 1.82)
INSULINS AND ANALOGUES (A10A)	0	0	7	2.69	0.10	(0.01 - 1.82)
OTHER PLAIN VITAMIN PREPARATIONS (A11H)	3	1.84	1	0.38	6.30	(0.60 - 66.41)
MINERAL SUPPLEMENTS (A12)	0	0	7	2.69	0.10	(0.01 - 1.82)
Heparin group (B01AB)	2	1.23	11	4.23	0.27	(0.06 - 1.25)
CARDIAC GLYCOSIDES (C01A)	7	4.29	4	1.54	3.30	(0.92 - 11.80)
Digitalis glycosides (C01AA)	3	1.84	1	0.38	6.28	(0.61 - 64.12)
Digoxin (C01AA05)	3	1.84	1	0.38	6.28	(0.61 - 64.12)
NERVOUS SYSTEM (N)	30	18.4	66	25.38	0.68	(0.41 - 1.11)
PSYCHOLEPTICS (N05)	5	3.07	22	8.46	0.34	(0.12 - 0.94)
ANXIOLYTICS (N05B)	4	2.45	18	6.92	0.33	(0.11 - 1.03)
Benzodiazepine derivatives (N05BA)	4	2.45	17	6.54	0.35	(0.11 - 1.09)
PSYCHOANALEPTICS (N06)	1	0.61	9	3.46	0.18	(0.02 - 1.49)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 28 (Cont´d). Influence of selected medications (p≤0.15) on urine pH. Magnitude of the association estimated by logistic regression. Fixed terms models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
RESPIRATORY SYSTEM (R)	3	1.84	20	7.69	0.25	(0.07 - 0.85)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES (R03)	1	0.61	11	4.23	0.17	(0.02 - 1.34)
Selective beta-2-adrenoreceptor agonists (R03AC)	0	0	6	2.31	0.12	(0.01 - 2.14)
OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES (R03D)	0	0	5	1.92	0.14	(0.01 - 2.59)
Xanthines (R03DA)	0	0	5	1.92	0.14	(0.01 - 2.59)
Theophylline (R03DA04)	0	0	5	1.92	0.14	(0.01 - 2.59)
COUGH AND COLD PREPARATIONS (R05)	1	0.61	7	2.69	0.21	(0.02 - 1.74)

*Adjusted for diet composition (daily vegetable, fruit and meat intake), height and weight, age, sex, study region, and vitamin C.

Table 29. Influence of some medications on urine pH. Magnitude of the association estimated by logistic regression: Step Wise Models

Medication	Constantly Acidic pH		Not constantly acidic pH			
	N = 163	%	N = 260	%	Odds Ratio Estimates*	(95% Confidence limits)
Respiratory System (R)	3	1,84	20	7,69	0,23	(0.07 - 0.81)
Psycholeptics (N05)	5	3,07	22	8,46	0,35	(0.12 - 0.96)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASE (R03)	1	0,61	11	4,23	0,15	(0.02 - 1.21)
Cardiac glycosides (C01A)	7	4,29	4	1,54	7,53	(1.63 - 34.7)
Systemic corticosteroids (single drugs) (H02A)	1	0,61	6	2,31	0,14	(0.01 - 1.62)
Hormone antagonists and related agents (L02B)	1	0,61	4	1,54	0,06	(0.002 - 1.46)
Anxiolytics (N05B)	4	2,45	18	6,92	0,16	(0.04 - 0.65)
Digitalis glycoside (C01AA)	3	1,84	1	0,38	6,30	(0.61 - 64.6)
Benzodiazepine derivatives (N05BA)	4	2,45	17	6,54	0,36	(0.11 - 1.13)
Digoxin (C01AA05)	3	1,84	1	0,38	11,3	(0.85 -150)
Captopril (C09AA01)	1	0,61	5	1,92	0,14	(0.01 - 1.89)

*Adjusted for diet composition (daily vegetable, fruit, and meat intake), height and weight, age, sex, study region, and vitamin C)

Results for the association between medications and urine pH. Magnitude of the association estimated by logistic regression: Step Wise

Table 29 shows the risk estimates for medications when building a logistic regression models forcing all confounders to enter the model, and entering all medications at the same digit level using a step wise strategy (p value to enter=0.15, p value to exit=0.20). Statistically significant association of medication and its influence on urine pH levels were found for drugs used on "Cardiovascular System". In this main group we found that 4.29% of patients with acidic urine pH were taking "cardiac glycosides" (OR=7.53, 95%CI: 1.64 – 34.7), where 1.7% of subjects took "digitalis glycoside" and more concretely "digoxin" (OR=11.3, 95%CI: 0.85 – 150). We also had 0.61% of subjects with acidic pH taking "Captopril" in this main group. Captopril use was not associated with acid urine pH levels (OR=0.14, 95%CI: 0.01 – 1.89).

"Systemic hormonal preparations" like "systemic corticosteroids (single drugs)" were taken by 0.61% of subjects with acid urine pH (OR=0.14, 95%CI: 0.01 – 1.62) and "hormone antagonists and related agents" used as antineoplastic agents were taken by 0.61% of patients with acid urine pH (OR=0.06, 95%CI: 0.002 – 1.46), and none of them was associated with acid urine pH levels.

Also, 18.4% of subjects with acid urine pH were taking drugs used in the "nervous system". We found that 3.07% of subjects with acid urine pH were taking "psycholeptics", founding in this group statistically significant influence on urine pH levels (OR=0.35, 95%CI: 0.12 – 0.96). Most of this psycholeptics taken by our study subjects were in the pharmacological subgroup of "anxiolytics" (OR=0.16, 95%CI: 0.04 – 0.65) and specially "benzodiazepine derivatives" (OR=0.36, 95%CI: 0.12 – 1.13).

Finally, we mention some drugs acting on "respiratory system". They were found to have a significant association with urine pH levels (OR=0.23, 95%CI: 0.07 – 0.81), where 0.61% of subjects with acid pH were taking "drugs for obstructive airways diseases" (OR=0.15, 95%CI:

0.02 – 1.22). Therefore, we can see that none of these drugs used on respiratory system were associated with acid urine pH levels.

6. Discussion

6. DISCUSSION

DISCUSSION OF RESULTS FOR CARDIAC GLYCOSIDES

Use of cardiac glycosides was found to be associated with having constantly acidic urine pH. Cardiac glycosides are mainly used in the treatment of congestive heart failure and cardiac arrhythmia. As our study is the first analyzing the association between use of such group of drugs and consistently acidic urine pH, we cannot directly compare our results with other studies. However, as discussed below, there is biological rationale to support our findings.

Use of cardiac glycosides in heart failure and the importance of potassium homeostasis

Congestive heart failure (HF) is the most frequent cause of hospitalization for patients older than 65 years, and continues to be a major public health burden among the ageing population. The mean of age of our study subjects is around 63 years old. Most patients with HF should be routinely managed with a combination of 3 types of drugs: a diuretic, an ACEI or an ARB, and a beta-blocker[134] and this treatment is associated with many limitations in clinical practice[135]. Patients with evidence of fluid retention should take a diuretic until a euvolemic state is achieved, and diuretic therapy should be continued to prevent the recurrence of fluid retention. Even if the patient has responded favorably to the diuretic, treatment with both an ACEI and a beta-blocker should be initiated and maintained in patients who can tolerate them because they have been shown to favorably influence the long-term prognosis of HF. Therapy with cardiac glycosides (mainly digoxin) as a fourth agent may be initiated at any time to reduce symptoms, prevent hospitalization, control rhythm, and enhance exercise tolerance. Its narrow therapeutic margin and its frequent interactions with other drugs make cardiac glycosides (mainly digoxin) difficult to use. Therefore, patients using cardiac glycosides are also usually using the above general

pharmacological treatment for HF, which has to be considered in the interpretation of our results.

To gain the maximum benefit from treatment, it is needed to individualize drug use and carefully monitor electrolytes. Symptomatic HF patients (New York Heart Association class III-IV) should be prescribed the lowest dose of diuretic necessary to maintain euvolemia. Mild hypokalemia may be corrected by the use of aldosterone receptor antagonists such as spironolactone or eplerenone. However, a more severe hypokalemia should preferably be corrected using K^+ supplement. Serum potassium levels should be frequently checked and maintained between 4.0 and 5.5mEq/l (mmol/l)[136]. Interestingly, drugs with a proven significant positive effect on mortality and morbidity rates in heart failure patients all increase plasma potassium concentration (Table 30). Thus, it may prove beneficial to pay more attention to hypokalemia and to maintain plasma potassium levels in the upper normal range. The more at risk of fatal arrhythmia and sudden cardiac death a patient is, the more attention should be given to the potassium homeostasis[137].

Table 30: Medications associated with hyperkalemia (Source: http://lpi.oregonstate.edu/infocenter/minerals/potassium/)

Medication Family	Specific medications
Potassium-sparing agents	Spironolactone, triamterene, amiloride
Angiotensin converting enzyme (ACE) inhibitors	Captopril, enalapril, fosinopril
Nonsteroidal anti-inflammatory agents (NSAID)	Indomethacin, ibuprofen, ketorolac
Anti-infective agents	Trimethoprim-sulfamethoxazole, pentamidine
Anticoagulant	Heparin
Cardiac glycoside	Digitalis poisoning
Anti-hypertensive agents	Beta-blockers, alpha-blockers
Angiotensin receptor blockers	Losartan, valsartan, irbesartan, candesartan

Hypokalemic status of cardiac patients and the acidification of urine

It has been known for nearly a century that cardiovascular diseases are associated with hypokalemia and potassium depletion in the heart[138]. Moreover, large-scale studies from recent decades[139-143] including, in total, more than 13,000 patients have shown that hypokalemia is present in 7% to 17% of patients with hypertension, acute myocardial infarction and heart failure. Also, up to 20% of hospitalized patients and up to 40% of patients on diuretics suffer from hypokalemia[144]. Whereas hypokalemia has been ignored by some investigators[145], the risk induced by hypokalemia in cardiac patients seems relatively well documented[146,147]. A recent study highlights the meaning of hypokalemia in heart failure underlining that maintenance of normal potassium (K^+) homeostasis has become an increasingly important limiting factor in the therapy of heart failure (HF). With the application of loop diuretics and digoxin, hypokalemia has become a frequent and feared side effect of treatment.

Mechanisms involved in the generation of hypokalemia and its effect on renal ammonia metabolism

Subjects suffering from heart failure and fluid retention taking digitalis glycosides have a combination of high aldosterone levels and an increased diuresis (more if is taken along with diuretics) that tends to produce significant increases in the secretion and excretion of potassium. It is important to differentiate between hypokalemia and potassium depletion. Hypokalemia is generally defined as a serum potassium concentration that is lower than 3.5 mmol/L, while potassium depletion is generally defined as reduced K^+ from total body stores. In cardiac patients, hypokalemia and potassium depletion are often caused by an increased loss of potassium through the kidneys due to nonpotassium-sparing diuretic therapy. This effect is, furthermore, often aggravated by insufficient potassium intake due to reduced appetite and the relatively low potassium content in modern food[137].

Hypokalemia is associated with increased ammoniagenesis and stimulation of net acid excretion by the kidney in both humans and experimental animals[14]. In this context, though with a not fully understood mechanism, there is increased ammonia excretion despite the development of metabolic alkalosis. Recent studies have shown that hypokalemia induces increased glutamine uptake into the proximal tubule, increasing the expression of the key ammoniagenic enzymes (that would tend to acidify urine), GA (glutaminase), GDH (glutamine dehydrogenase) and PEPCK (phosphoenol pyruvate carboxykinase)[7,14]. At the same time, a hypokalemic status can also increase the expression of Rh glycoprotein (Rhcg) an ammonia transporter in the collecting duct[7] (see Figures 8 and 9, and Table 2). If Rhcg expression is associated with systemic acid-base homeostasis, hypokalemia should decrease its expression due to the development of alkalosis. These observations indicate that the enhanced Rhcg expression and collecting duct ammonia excretion could be regulated through mechanisms independent of acid-base homeostasis. The stimulation of ammoniagenesis in response to acidosis or hypokalemia is likely to be activated by either intracellular acidic pH or other factors. Recent studies have also demonstrated that the increase in urinary ammonia excretion even developed within 2 days of potassium deprivation, when the plasma potassium level was within normal limits[14]. Thus, the excretion of ammonia by this mechanism would tend to acidify urine in a context independent of blood acid-base homeostasis compensatory mechanisms.

Activity of Na^+/K^+-pumps in cardiac patients and its relation to potassium homeostasis and response to digitalization

In addition to hypokalemia due to potassium depletion, shift of potassium into stores may cause a rapid reduction in serum potassium concentration to below 3.5 mmol/L, what is particularly relevant in cardiac patients[137]. This may result from stimulation of the activity of Na^+/K^+ pumps in skeletal muscles. In cardiac insufficiency, the decrease in the concentration of Na^+/K^+-pumps in the myocardium is over a wide range correlated to the concomitant reduction in ejection fraction. The regulatory and pathophysiological changes in the activity

and concentration of Na^+/K^+-pumps are important for the contractile function of skeletal muscle and heart as well as for K^+ homoeostasis and the response to digitalization. The digitalis glycosides exert their effects in patients with HF by virtue of their ability to inhibit sodium-potassium (Na^+-K^+) adenosine triphosphatase (ATPase)[148]. Inhibition of this enzyme in cardiac cells results in an increase in the contractile state of the heart, and for many decades, the benefits of digitalis in HF were ascribed exclusively to this positive inotropic action. However, recent evidence suggests that the benefits of digitalis may be related in part to enzyme inhibition in noncardiac tissues. Inhibition of Na^+-K^+ ATPase in vagal afferent fibers acts to sensitize cardiac baroreceptors, which in turn reduces sympathetic outflow from the central nervous system[149,150]. In addition, by inhibiting Na^+-K^+ ATPase in the kidney, digitalis reduces the renal tubular reabsorption of sodium[151]; the resulting increase in the delivery of sodium to the distal tubules leads to the suppression of rennin secretion from the kidneys[152]. These observations have led to the hypothesis that digitalis acts in HF primarily by attenuating the activation of neurohormonal systems and not as a positive inotropic drug[153]. Low serum K^+ in HF may be also a marker of increased neurohormonal activity and disease progression (see figure 10). Hence, congestive heart failure is often associated with high levels of circulating adrenaline and noradrenaline. Because of stimulation of the beta adrenoceptors in muscle and liver, this leads to hypokalemia, which predisposes to ventricular arrhythmia, and increased ammoniagenesis and stimulation of net acid excretion by the kidney [154].

Therefore, a predominant hypokalemic status in patients using cardiac glycosides would drive to acidic urine pH, which can then be partly explained by both: heart failure condition by itself, and its common treatment (including cardiac glycosides and other medications) with hypokalemia as a common adverse effect. In fact, standard digitalization itself, with a dose of digoxin sufficient to give a plasma concentration of 1.2 nM, can induce a significant decreases in whole-body K^+ and muscle K^+ of 8 and 6% respectively[155].

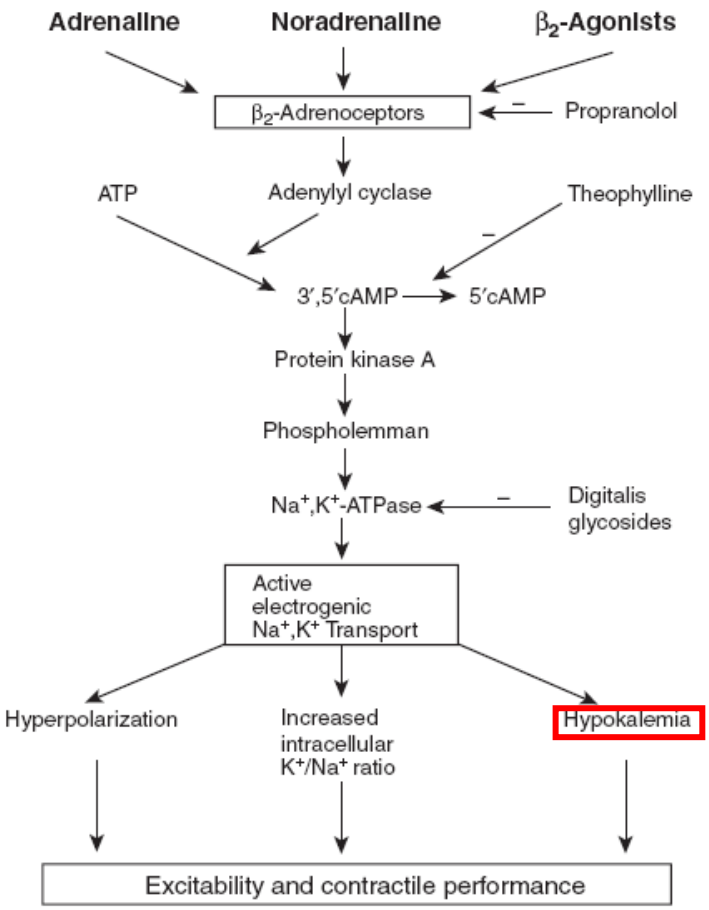

Figure 10. Sequence of events in the action of catecholamines and beta2 agonists on active Na+,K+ transport, Na+,K+ distribution and contractile performance in skeletal muscle. Adapted and modified from Clausen T (2009)

Also, there are situations where inhibition of Na^+/K^+-pumps in the membrane of cells by cardiac glycosides can lead to hyperkalemia. However, as said above, standard digitalization, with a dose of digoxin sufficient to give a plasma concentration of 1.2 nM, induces significant decreases in whole-body K^+ and muscle K^+ of 8 and 6% respectively[155]. It is well known that human whole-body K^+ homeostasis depends on the renal excretion of K^+. Indeed, the kidneys are essential for the long-term regulation of whole-body K^+ content, and renal failure leads to hyperkalemia. However, several tissues contribute to the acute short term regulation of the K^+ concentration in plasma and the extracellular space. Human skeletal muscles play an important role in this regulation, containing the largest single pool of K^+ in the body (2600 mmol, 46 times the total K^+ content of the extracellular space). Intense

exercise may double arterial plasma K^+ in one minute. This is because of excitation induced release of K^+ from the working muscle cells via K^+ channels. This hyperkalemia is rapidly corrected by reaccumulation of K^+ into the muscle cells via Na^+/K^+ pumps, often leading to hypokalemia. Already long ago, it was observed that in trained individuals, the exercise-induced hyperkalemia was considerably reduced. More recently, it was shown that following sprint training, the exercise-induced rise in plasma K^+ was 19% lower than before, and this was associated with an increase in the content of Na^+/K^+ pumps in skeletal muscle[156]. This increase improves the capacity for the clearance of K^+ from plasma and extracellular space. It has repeatedly been demonstrated that training increases the content of Na^+/K^+ pumps in human skeletal muscles[157,158]. Conversely, downregulation of the Na^+/K^+ pumps in skeletal muscle as seen in cardiac failure, myotonic dystrophy or McArdle disease increases the exercise-induced hyperkalemia[155].

Another implication of a reduction in the concentration of Na^+/K^+-pumps in skeletal muscle is that the muscular pool of digitalis receptors is decreased. Thus, after the administration of digitalis glycosides, a larger fraction of the dose given will be available for distribution in the extracellular volume, leading to a higher plasma concentration. In keeping with this it is a well-known clinical experience that K^+-deficient patients are more sensitive to digitalization[159]. This relation has been explored in some experiments[160] and illustrates the major influence of the large muscular pool of digitalis glycoside receptors on the availability of digitalis glycosides in plasma and offers an explanation for the increased sensitivity to digitalis in patients suffering from K^+ deficiency. It should be added that since K^+ interferes with the binding of digitalis to the Na^+/K^+-pump, the hypokalaemia associated with K^+ deficiency favours the binding of digitalis to all cells and increases the risk of intoxication. So a selective inhibition of the Na^+/K^+ pumps as induced by intoxication with digitalis glycosides leads to impairment of K^+ uptake into the skeletal muscles. The ensuing hyperkalemia is a typical finding following an overdose of cardiac glycosides[161]. A study of 91 patients with digoxin intoxication showed that those with plasma K^+ above 6.2 mM (26%) died[162].

Therefore, hypokalemia is commonly found in cardiac patients. As said above, the hypokalemic status could be enhanced by the direct effect of standard digitalization, and it is a common adverse effect of HF treatment. A predominant hypokalemic status, that would significantly increases renal ammonia production and excretion, could explain the development of a constant acidification of urine as we have observed.

Acid-base disturbances in patients suffering from heart failure and the acidification of urine

Disturbance in acid-base balance is commonly observed in patients with heart failure. The most common disturbance is metabolic alkalosis combined with hypokalemia, and as explained above in this section, this situation enhances the acidification of urine. Compensatory mechanisms, coexistence of independent acid-base disorders and changes in electrolytes complicate acid-base balance in the individual patients. As acid-base disturbances have harmful effects on the cardiovascular system, precise diagnosis and proper treatment are highly important[163].

Also, when pulmonary edema develops, carbon dioxide retention occurs, resulting in respiratory acidosis[163], and a decreased tissue oxygen delivery may also produce lethal lactic acidosis[163]. Excess ventilation during exercise with accompanying dyspnea is characteristic of chronic heart failure (CHF), and these patients often exhibit increased minute ventilation (Ve) relative to the Vco_2, depending upon the fall in pH and pCO_2, compared with normal subjects[164,165]. So patients with CHF at resting conditions are often characterized by high pCO_2 and fall in pH (mainly when pulmonary edema develops). In this context of pulmonary edema, the acidification of urine at resting conditions would be enhanced, while ventilation when exercising is increased compared to healthy subjects[164].

Cardiac conditions symptoms and acidic urine

The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral

edema. Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they do not necessarily dominate the clinical picture at the same time. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema and report few symptoms of dyspnea or fatigue. Because not all patients have volume overload at the time of initial or subsequent evaluation, the term “heart failure” is preferred over the older term “congestive heart failure”[166].

Patients perceive different symptoms of heart failure decompensation[167], but frequently presents with shortness of breath with exertion, orthopnea, and paroxysmal nocturnal dyspnea. For instance, in a recent study, from 371 patients suffering from HF, the dominant symptom identified was difficulty breathing by 193 (52%) patients, fatigue by 118 (32%), and abdominal discomfort and swelling each by 30 (8%) patients[167]. Risk factors for acute decompensation include high dietary salt intake, medication noncompliance, cardiac ischemia, dysrhythmias, renal failure, pulmonary emboli, hypertension, and infections[168]. A dominant difficulty of breathing in the symptomatology of patients suffering from heart failure could enhance the acidification of blood due to a decrease excretion of CO_2, and this could make these subjects more suitable to develop constant acidic urine.

Several other studies have shown associations between cardiac diseases and shortness of breath. For example, obstructive sleep apnea (OSA) has adverse effects on blood pressure, cardiovascular status, and mortality. Patients who have congestive heart failure have a high prevalence of sleep-disordered breathing, with OSA occurring in 30% of such patients and Cheyne-Stokes respiration in 40%[169]. Also, some patients do not improve or experience rapid recurrence of symptoms while on standard medication for HF. Refractory heart failure (RHF) is characterized by marked symptoms at rest or on minimal exertion despite maximal medical therapy such as rest, sodium restriction, the status of digitalization, and mercurial diuretics[170].

It should be added that due to dietary factors (diet poor on vegetables and fruits) related to the development of the medical conditions for which cardiac glycosides are prescribed, often

aggravated by insufficient potassium intake due to reduced appetite, the relatively low potassium content in modern food, and together with a low exercise activity, may also contribute in the enhancement of urine acidification[61,171].

DISCUSSION OF RESULTS FOR ANXIOLYTICS

Psycholeptics (mainly the group of anxiolytics) showed a significant association with having non-constantly acidic urine pH in our study subjects. To date, this is the first study to report such association, which makes impossible the comparison with other studies. We discuss below some possible mechanisms to explain our findings that might include from a direct effect of anxiolytics in the acid-base balance, to a more likely scenario where anxiolytics use just reflect the underlining effect in urine pH through a hyperventilation mechanism when present in anxiety disorders for which they are prescribed for.

Most of the anxiolytics reported by our study subjects were benzodiazepine derivatives. Benzodiazepines are prescribed for short and long-term relief of insomnia, and moderate or severe anxiety, that frequently are associated with depression. There are many types of anxiety disorders that include panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, social anxiety disorder, specific phobias, and generalized anxiety disorder. The physical effects of anxiety may include heart palpitations, tachycardia, hyperventilation, muscle weakness and tension, fatigue, nausea, chest pain, shortness of breath, headache, stomach aches, or tension headaches. As the body prepares to deal with a threat, blood pressure, heart rate, perspiration, blood flow to the major muscle groups are increased, while immune and digestive functions are inhibited (the *fight or flight* response). External signs of anxiety may include pallor, sweating, trembling, and pupillary dilation. For someone who suffers anxiety this can lead to a panic attack.

Anxiety disorders and chronic hyperventilation

Regarding the acid-base status of subjects suffering from anxiety disorders, it is important to highlight the role of chronic hyperventilation, with multiple symptomatology due to respiratory alkalosis, that is frequently associated with emotional disturbances such as anxiety, panic and depression[172], or with psychosomatic disorders such as irritable bowel, effort syndrome and chronic pain. A possible explanation for our findings could be that

respiratory alkalosis causes a decrease in the partial pressure of carbon dioxide (pCO_2) and an increase of bicarbonate (HCO_3^-) renal excretion that would contribute to the alkalinization of urine in patients suffering from anxiety disorders[173].

The literature on “hyperventilation syndrome” suggests that acute hyperventilation rarely possess diagnostic or therapeutic problems. Chronic hyperventilation, however, with vague and multiple symptomatology due to respiratory alkalosis and increased breathing work, is often overlooked or misinterpreted, though it is a very common disorder of the general patient population[174]. As said before, chronic hyperventilation is frequently associated with anxiety, panic and depression. Studies on the pathogenesis of panic disorder (PD) have concentrated on panic attacks. However, PD runs a chronic or episodic course and panic patients remain clinically unwell between attacks[175]. Panic patients chronically hyperventilate, but the implications of this are unclear. Regarding the relationship between panic, hyperventilation and anxiety in a chronic status, the literature provides evidences and hypotheses to have into account and to better predict the acid-base status of individuals experiencing from these disorders: First, provocation of panic experimentally has indicated that several biological mechanisms may be involved in the onset of panic symptoms. Evidence from provocation studies using lactate, but particularly carbon dioxide (CO_2) mixtures, suggests that panic patients may have hypersensitive CO_2 chemoreceptors. Klein proposed that PD may be due to a dysfunctional brain's suffocation alarm and that panic patients hyperventilate to keep pCO2 low. Second, studies of panic patients in the non-panic state have shown EEG (electroencephalograph) abnormalities in this patient group, as well as abnormalities in cerebral blood flow and cerebral glucose metabolism. These abnormalities can be interpreted as signs of cerebral hypoxia that may have resulted from hyperventilation. Third, cerebral hypoxia is probably involved in the causation of symptoms of anxiety in sufferers of chronic obstructive pulmonary diseases. By chronically hyperventilating, panic patients may likewise be at risk of exposure to prolonged periods of cerebral hypoxia which, in turn, may contribute to the chronicity of their panic and anxiety

symptoms. Fourth, chronic hyperventilation may engender a self-perpetuating mechanism within the pathophysiology of PD, a hypothesis which warrants further studies of panic patients in the non-panic state.

The level of a hyperventilation is thought to be higher among patients suffering from PD. Some findings lend support to a group of studies showing differences in respiratory function between panic disorder and other anxiety disorders populations, providing preliminary support for the presence of a distinct "hyperventilation subtype" of panic disorder[176]. Hyperventilation (i.e. CO_2 exhalation in excess of metabolic demands) has been proposed as being either an etiologic[177] or a specific associated feature of panic disorder (PD)[178]. Several studies comparing resting end-tidal CO_2 ($EtCO_2$) levels between PD patients and normal controls (NC) have documented significant differences[179-181], and recent findings seem to suggest a respiratory preparedness for stress (ie, bronchodilation) in PD patients[182]. However, it has been argued that low $EtCO_2$ in panic patients may only reflect the profound distress of an anxiety condition rather than being specific to panic disorder per se. For example, psychological distress is known to produce increases in respiration rate[183]. More recent studies have looked at $EtCO_2$ levels in PD patients *vs*. other anxiety disorder patients. De Ruiter et al.[184] failed to find significant differences between groups of PD and generalized anxiety disorder (GAD) patients, during either: rest, hyperventilation, exercise, or CO_2 inhalation conditions. However, no measures of subjective distress were taken, thus making the similarities difficult to interpret. Holt and Andrews[185] found their sample of PD patients to have higher baseline levels of anxiety than their comparison groups of social phobics, GAD patients, and NCs, but found no differences in $EtCO_2$. The authors concluded that their baseline $EtCO_2$ data may have been atypical. Thus, the issue of general distress resulting in increased ventilation rate, *vs*. the specific role of hyperventilation in panic disorder remains a controversial point. A study better addressed the results of such differences[176], where seventeen panic disorder patients (PD), 18 patients with generalized anxiety disorder (GAD), and 20 normal control (NC) subjects were administered a psychophysiological evaluation

composed of baseline, stressor, and recovery phases. Panic patients were measured for the severity of respiratory symptoms during panic attacks. End-tidal CO2 (EtCO2) and respiration rate were measured throughout the psychophysiological evaluation. The results show that PDs demonstrated significantly lower baseline EtCO2 levels than the GADs and NCs, in spite of being equivalent to GADs on baseline anxiety levels. Moreover, panic patients reporting a high level of respiratory symptoms during panic attacks seemed to account for the bulk of observed differences. A more recent study summarizes new findings concerning the respiratory subtype (RS) of panic disorder (PD) since its first description, where some characteristics, such as the increased sensitivity to CO_2 and the higher familial history of PD, clearly distinguish the RS from the non-RS. Nevertheless, there are also controversial findings that need future researh[186].

Explanations for the discrepancy in findings regarding resting measures of respiratory function in panic disorder have generally taken two forms. First is the proposal that a biased population sampling resulted in panic group compositions that were either high or low in respiration-related processes[187]. Based on this suggestion, it is possible that a hyperventilation subtype of panic disorder may exist, and the question then becomes one of differentiating the subtypes. For example, we mentioned before that Klein[188] proposed a "suffocation alarm theory" of panic attack that suggests two classes of patients with panic disorder: a) individuals who report intense breathing difficulty during panic, and b) individuals who report little or no breathing difficulty during panic. There are no published studies delineating methods on how to classify individuals who panic into the categories suggested by Klein, although one such method may be to use the self-reported incidence of respiratory symptoms during panic on standardized psychometric instruments (e.g., the Panic Symptom Report)[189]. A second proposal for the contradictory findings of past research is that panic and anxiety comparison groups have not been equated for, or otherwise controlled for baseline levels of anxiety. It is possible that higher arousal levels in panic subjects are responsible for

measured differences in respiratory function, rather than factors specific to panic disorder per se[187,190].

The role of pCO_2 in anxiety disorders

Results of most studies provide some controversial findings by measured differences in respiratory function, as controversial $EtCO_2$ levels in PD or differences in respiratory pattern between GAD and PD, where several mechanisms are involved in the onset of symptoms. Some hypothesis suggest that panic patients may have hypersensitive CO_2 chemoreceptors, (dysfunctional brain´s suffocation alarm in panic patients that trigger hyperventilation to keep pCO2 low), or/and a hyperventilation subtype that need future research. It is important to understand whether blood carbon dioxide (pCO_2) levels generally vary inversely with minute volume. For example, a person with increased minute volume (e.g. due to hyperventilation) should demonstrate a lower blood carbon dioxide level. Although minute ventilation (VE) is easily measured, it does not provide sufficient information for assessing the adequacy of alveolar ventilation (VA), the component that affects gas exchange. The tidal volume and the respiratory rate do not give any clue as to how much air is ventilating dead space vs. alveolar space. Even if dead space ventilation (VD) and VA were measurable, the measurements would not indicate how much carbon dioxide was being produced in the body or how much VA was necessary to eliminate the carbon dioxide production. Low pCO_2 (hypocapnia) defines a state of hyperventilation. It has to be clear that someone who is breathing fast and deep may be hyperventilating in the physiologic sense (i.e., has a low pCO_2) but then again may also be hypoventilating (has a high pCO_2). The latter could come about if most of the minute ventilation were going to dead space with very little left over for VA (this situation may arise in severe chronic obstructive pulmonary disease when there is a large amount of dead space from ventilation-perfusion imbalance).

Intracellular pH is strictly regulated in brain cells, and also marginal aberration of H^+ concentration may cause big functional deviation in neurons[191]. Carbon dioxide concentration

is one of the most important factors which influence the intra- and extracellular pH, because CO_2 is extremely diffusible and in this way we can rapidly send or extract H^+ ions to or from all tissues, all cells (nearly the same time) drawing breath rarely or frequently. CO_2 passes very quickly through the cell membranes and it forms carbonic acid with H_2O which gives H^+ ions. On the other hand ions get slowly through membranes, even H^+-ion itself. That is because they have electric charge and become hydrated, and this multiplies their radius, but CO_2 does not have either of them and it is soluble in lipids.

If we take our breath deeply or frequently our pulse speeds up proving that CO_2 has left the pacemaker cells of heart, and the alkalic cytoplasm allowes Ca^{2+} to enter in the cytosol. If we keep on this kind of breathing for a long time, our pulse will slowly come back to the incipient frequency because the organism compensates the alteration of pH in the cytosol. The lack of H^+ in cytosol increases conductance of Ca^{2+} and some other ions[192], thus it increases contraction, metabolism and O_2 requirement[193], and also increases excitability of neurons in the peripherium and in the brain[194]. All these events can be explained by the simple fact that lack of H^+ (=alkalosis) increases transmembrane conductance of ions and (consequently) increases active ion-pumping mechanisms too (because the original ion-status has to be restored).

Alteration of carbon dioxide concentration can appear in the whole organism at the same time. If it endures for a long time (several hours to one week), the organism starts to “compensate”. Stability of extra- and intracellular pH is of high priority. Renal function and tissular buffer mechanisms (mostly) restore the pH in the cytosol of the cells and in the extracellular space, but the concentration of other ions is altered in the cytosol at the same time. The development of the new ionmilieu needs 5-7 days[195]. Then chronic hypocapnia or hypercapnia is followed by cascades which alter the whole ionmileu in the cells, they may alter even the neurotransmitter/endocrine status[196]. The fact that intracellular pH is very strictly regulated does not mean it cannot go wrong. It seems like human is a specie especially endangered by the long-term alteration of carbon dioxide level. This is because

he/she becomes hypo- or hypercapnic not only because of organic diseases, but of mental disorders too, and – most importantly — because of his/her behaviour. The last one is dangerous, because it may cause diseases of civilization. It is frequently asserted that it is the "stress of life" itself that causes diseases of civilization (induced by "stress-hormones")[197]. In stress situations wild animals behave according to their instincts. The main behaviour is – according to Cannon – the "fight or flight" response, which is a hyperarousal condition. In this acute stress there is a strong catecholamine (adrenaline, noradrenaline) rush and an acute hypocapnia as well. Wild animals during this hyperarousal condition will fight or flee, they take physical exercise, and this physical activity/muscle-work results in increased carbon dioxide production – this way they get a good chance to restore the decreased carbon dioxide level. Contrarily human acute stress response mostly differs from that because of their learnt behaviour. They mostly restrain their temper, the physical activity will fail and the hyperventilation/hypocapnia endures long causing a range of ion-movements through membranes and causing metabolic and endocrine alterations and illnesses because of the alteration of "milieu interieur". Namely, diseases of civilization are caused by the distress evoked by the lack of instinctive reaction to stress. Nowadays some researchers start to discover the theoretical significance of hyperventilation in stress induced illnesses[198].

According to Tenney there is a feedback mechanism between carbon dioxide level and catecholamine output of the organism[199]. In alkalosis condition catecholamine responsibility and sympathicotonia increases (although catecholamine output slightly decreases)[198-200]. Catecholamines, e.g. noradrenaline increase the Na^+/H^+ exchange in the cells[201] that causes alkalosis in the cytosol, similarly to the effect of hypocapnia. These catecholamines take effect (at least partly) through causing intracellular alkalosis[202]. Cannon's "fight or flight" response means a strong sympathicotonia/ hyperarousal, because both catecholaminemia and hyperventilation cause alkalosis in the cytosol.

Decreased H^+ concentration (intracellular alkalosis, i.e. decreasing carbon dioxide concentration in the case of acute hyperventilation) increases transmembrane Ca^{2+}

conductance, thus increases the amount of Ca^{2+} entering into the cytosol[191]. Catecholamines activate the Na^{+}/H^{+} exchange mechanism, causing intracellular alkalosis as well. Therefore everything that decreases the concentration of intracellular (cytosolic) Ca^{2+} and/or H^{+} concentration — in resting/ basal state of cells — increases the Ca^{2+}-conductance in neurons and the excitability. H^{+} seems to be the most important ion which modifies Ca^{2+}-conductance, it can be considered a modifier of second messenger Ca^{2+}. E.g. intracellular alkalosis, acute hypocapnia, thyroxin and catecholamines increase arousal. Very simply written: the amount of Ca^{2+} entering into the cytosol determines how strong the response is given by the neuron (e.g. during neurotransmitter release)[196,203]. Ca^{2+} enters the cytosol partly through the plasma membrane as a result of action potential, partly from the intracellular organelles (from sacroplasmic reticulums and mitochondria). The bigger the Ca^{2+} extracytosolic/intracytosolic (EC/IC) chemical potential is, the larger amount of Ca^{2+} will enter into the cytosol. That is why Ca^{2+} pumping mechanisms (which need ATP energy) have great importance.

Panic attack is coursing with a cascade of events where hyperventilation has different roles in different times. Chronic hyperventilation is probably a precondition of (respiratory subtype) panic attack[202]. Chronic hyperventilation can be generated by either organic diseases (e.g. asthma bronchiale) or mental conditions (e.g. sighing or crying for a tragedy). Compensational mechanisms set off metabolic acidosis that neutralizes hyperventilational alkalosis, this compensational process last at least for a week. In the state of compensated hypocapnic alkalosis extra- and intracellular pH stays in the normal range. The depressed pCO_2 level starts to go up to the normal level (or slightly higher) before the attack. The elevating carbon dioxide promptly diffuses into cells and causes acidosis, which increases catecholamine release from different cells (e.g. noradrenaline release from locus coeruleus)[204]. On the other hand, elevating carbon dioxide level also evokes acute hyperventilation (through a brainstem reflex), which may be more vigorous than previously. At this point hypercatecholaminemia (induced by previous acidosis) and alkalosis (abruptly decreasing pCO_2 level) evolve at the same time. Alkalosis multiplies CNS-responsiveness to

catecholamine levels, and it lasts for several minutes to break down catecholemines. This coexistence means an intense sympathicotonia, a very high arousal (panic attack). According to this panic theory intra- and extracellular pH is thoroughly compensated before the attack, but the acidosis would be overcompensated by acute hypocapnic alkalosis during the attack. The main problem is that the different compensational mechanisms work out at different rates. Carbon dioxide level can change in the whole organism in a few seconds, the elimination of catecholamines lasts for several minutes, and the clearing of blood from metabolic ("titratable") acidity takes at least one week. This is one of the many reasons there is no perfect compensational mechanism.

Acute and chronic hyperventilation may cause alterations and symptoms in almost any organs, not only in the CNS[193,205]. GAD (generalized anxiety disorder) is pathogenetically also like PD, but with important differences. pCO_2 level shows great variability in PD (mainly in the hypocapnic range), but it seems to be around the normal level in case of GAD patients[206]. Respiration is extremely unstable and irregular in PD. Respiratory variability in GAD is lower than in PD, though it is higher than physiologically. Alteration of pCO_2 level makes catecholamine levels fluctuate because of altering pH. Actual catecholamine levels interfere with actual pCO_2 levels, which results in arousal alterations (like PD). Namely both pCO_2 and catecholamine levels are fluctuating but with different rates – their effects on arousal sometimes added together. Changes of carbon dioxide and catecholamine level may affect on most neurons similarly. Neurons in the brain are working together. Those neurons linked to each other in a row are able to multiply both hypo- and hyperarousal.

It has been supposed that there is a fluctuating pCO_2 level slightly around the normal values at GAD patients. Intracellular pCO_2/pH and catecholamine level would keep changing permanently, causing more or less arousal than in the healthy controls. That is why arousal fluctuates permanently, even dysthymia can arise[207]. It has been argued that every hyperarousal condition involves hypoarousal periods too. One of the reasons for this may be that pH elevation (and pCO_2 decrease) is predominant and has to be corrected from time to

time (cytosolic pH is limited in a narrow range even in pathological conditions). This hypothetic situation is compatible with our observed results on the association between use of anxiolytics and development of not constantly acidic urine pH.

GAD means permanently fluctuating ventilation and altering arousal, which hypo- and hyperarousal conditions affect each other and may cause vicious circles through psychogenic mechanisms. This fluent alteration may result in depression and/or psychosomatic disorders.

Effects of psycholeptics in the Respiratory system

Regarding the effect of these psycholeptics, aside of their sedative effects, barbiturates and benzodiazepines are also known to have respiratory depressant effects. Differing effects of the anxiolytic agent buspirone and diazepam on control of breathing have been elucidated in few studies[208,209]. These studies compared ventilatory effects of the nonsedating anxiolytic buspirone with those of the sedating anxiolytic diazepam. Diazepam had no effect on resting ventilation but depressed response to CO2. In summary, buspirone did not cause the depression of respiratory center chemosensitivity that was seen with diazepam and produced less depression of load compensation in normal subjects. Changes in respiratory pattern and arterial pCO2 after three repeated intravenous sedative doses of midazolam 0.05 mg/kg or diazepam 0.15 mg/kg were shown in eight healthy male volunteers in a randomized double-blind crossover design in other study[210]. Both drugs caused equal changes in breathing pattern with a decrease in tidal volume, an increase in respiratory rate and unaltered minute ventilation. These alterations in breathing pattern were associated with CO2 retention. Despite increased plasma drug concentrations, subsequent doses did not cause further changes in respiratory variables except for an increase in pCO2 after the second dose of midazolam.

To conclude this section, to explain our observed association between use of psycholeptics (mostly anxiolytics) and non-acidic urine, we believe there is a major explanation available:

the development of a low blood pCO_2 due to a predominant hyperventilation status on patients suffering from anxiety disorders. This would normally drive to a respiratory alkalosis, which would enhance the alkalinization of the urine. This mechanism would have a stronger impact in urine pH than the direct effect of anxiolytics as depressants of the respiratory system.

DISCUSSION OF RESULTS FOR DRUGS FOR THE RESPIRATORY SYSTEM

Finally, drugs acting on the respiratory system were found to have a significant association with not having acidification of urine, with a suggestion of a specific association among users of drugs for obstructive airway diseases. Again, no specific studies are available in the literature on the role of respiratory drugs and consistently acidic urine pH. We discuss in the sections below the biologic mechanisms that would explain our findings, triggered by the medication itself, or by the disease for which they are prescribed for.

Chronic obstructive pulmonary disease (COPD) is the occurrence of chronic bronchitis or emphysema, a pair of commonly co-existing diseases of the lungs in which the airways narrow over time. This limits airflow to and from the lungs, causing shortness of breath (dyspnea). In clinical practice, COPD is defined by its characteristically low airflow on lung function tests. In contrast to asthma, this limitation is poorly reversible and usually gets increasingly worse over time.

Chronic bronchitis and asthma treatments: the effect of the ATC group of "drugs for obstructive airways diseases" on urine pH

Chronic bronchitis, a type of chronic obstructive pulmonary disease, is defined by a productive cough that lasts greater than three months each year for at least two years in the absence of other underlying disease. Symptoms of chronic bronchitis may include wheezing and shortness of breath, especially upon exertion and low oxygen saturations. The cough is often worse soon after awakening and the sputum produced may have a yellow or green color and may be streaked with specks of blood. Chronic bronchitis is treated symptomatically and may be treated in a nonpharmacologic manner or with pharmacologic therapeutic agents. Typical nonpharmacologic approaches to the management of COPD including bronchitis may include: pulmonary rehabilitation, lung volume reduction surgery, and lung transplantation. Inflammation and edema of the respiratory epithelium may be

reduced with inhaled corticosteroids. Wheezing and shortness of breath can be treated by reducing bronchospasm (reversible narrowing of smaller bronchi due to constriction of the smooth muscle) with bronchodilators such as inhaled long acting β_2-adrenergic receptor agonists (e.g., salmeterol) and inhaled anticholinergics such as ipratropium bromide or tiotropium bromide. Mucolytics (also known as expectorants) may have a small therapeutic effect on acute exacerbations of chronic bronchitis.

Asthma is the most common reason for presenting to emergencies with shortness of breath. It is the most common lung disease in both developing and developed countries affecting about 5% of the population. Other symptoms include wheezing, tightness in the chest, and a non productive cough[211]. Medications used to treat asthma are divided into two general classes: quick-relief medications used to treat acute symptoms; and long-term control medications used to prevent further exacerbation. Fast–acting: short-acting beta$_2$-adrenoceptor agonists (SABA), such as salbutamol are the first line treatment for asthma symptoms. Anticholinergic medications, such as ipratropium bromide, provide additional benefit when used in combination with SABA in those with moderate or severe symptoms. Anticholinergic bronchodilators can also be used if a person cannot tolerate a SABA. Long–term control: corticosteroids are generally considered the most effective treatment available for long-term control. Inhaled forms are usually used except in the case of severe persistent disease, in which oral corticosteroids may be needed. Long-acting beta-adrenoceptor agonists (LABA) such as salmeterol and formoterol can improve asthma control, at least in adults, when given in combination with inhaled corticosteroids. Leukotriene antagonists may be used in addition to inhaled corticosteroids, typically also in conjunction with LABA. Evidence is insufficient to support use in acute exacerbations. External factors can influence on how severe asthma responds to medical treatment, though the mechanisms are not fully understood[212].

Drugs used in the respiratory system, such as ATC group of “drugs for obstructive airways diseases”, improve lung function in patients with lung diseases, such as asthma, emphysema

or chronic bronchitis, by improving alveolar ventilation (increase excretion of CO_2). The increased excretion of CO_2 prevents the acidification of blood and consequently would prevent the acidification of urine.

We found that from 66 subjects with chronic bronchitis, 10 were using “drugs for obstructive airway diseases” during urine pH measurements, and two of them (20%) had acidic urine pH. Among the remaining 56 subjects suffering from bronchitis that were not using “drugs for obstructive airway diseases”, 21 (37.5%) had acidic urine pH (Table 31). This suggests that these drugs could help to prevent acidic urine among subjects with bronchitis. Interestingly, it can be also observed that all subjects not suffering from bronchitis and using “drugs for obstructive airway diseases” during urine pH measurements had not constantly acidic urine pH, showing a significant association between these drugs and the generation of not constantly acidic urine pH (Table 31). This observation is compatible with a direct effect of these drugs on urine pH.

Table 31: Constantly acidic urine pH by use of “drugs for obstructive airway diseases” in chronic bronchitis

Subjects taking “drugs for obstructive airway diseases”	Yes (n)	Percent	No (n)	Percent	p
Subjects suffering from bronchitis					
Not constantly acidic urine pH	8	80	35	62.5	
Constantly acidic urine pH	2	20	21	37.5	0.28
Subjects not suffering from bronchitis					
Not constantly acidic urine pH	6	100	266	59.5	
Constantly acidic urine pH	0	0	181	40.5	0.04

Also, it can be observed that from 46 asthmatic subjects, 9 were using drugs for obstructive airway diseases during urine pH measurements and only one of them (11.1%) had acidic urine pH (maybe due to a not well compensated asthma symptomatology). However among

the remaining 37 asthmatic subjects that were not using drugs for obstructive airway diseases, 16 (43.8%) had acidic urine pH (Table 32). This suggests that drugs for obstructive airway diseases could help to prevent acidic urine among subjects with asthma. From seven subjects not suffering from asthma and using drugs for obstructive airway diseases, only one (14.3%) showed acidic urine, highlighting again (but with less significance than in Table 31) the possible importance of the direct effect of these drugs on urine pH.

Table 32: Constantly acidic urine pH by use of "drugs for obstructive airway diseases" in asthma

Subjects taking "drugs for obstructive airway diseases"	Yes (n)	Percent	No (n)	Percent	p
Asthmatics subjects					
Not constantly acidic urine pH	8	88.9	21	56.2	
Constantly acidic urine pH	1	11.1	16	43.8	0.07
Not asthmatics subjects					
Not constantly acidic urine pH	6	85.7	281	60.2	
Constantly acidic urine pH	1	14.3	186	39.8	0.17

Role of ventilatory drive in asthma and chronic obstructive pulmonary disease (COPD): pathophysiologic features and acid-base disturbances

Asthma and COPD are chronic inflammatory disorders of the airways in which many different types of cellular elements play roles. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness and coughing[213]. There is increasing recognition that psychological factors influence the onset and course of asthma. A part of the enhanced action in CO_2 excretion by the lungs from drugs used for obstructive airway diseases, asthmatics and COPD patients may also have an increased excretion of CO_2 through a hyperventilation status that could enhance the alkalinization of urine, while suffering airways inflammation. The ventilatory drive has been found to play a key role in

determining the severity of asthma and COPD[214]. The ventilatory drive is affected by several factors such as chemosensitivity, basal arterial oxygen or carbon dioxide tension, mechanical impedance, and respiratory muscle dysfunction.

The response of asthmatic airways to irritant stimuli is twofold: bronchoconstriction and airway inflammation[215]. The inevitable mechanical consequence of bronchoconstriction is hyperinflation of the lungs, a phenomenon that helps to maintain airway patency at the expense of increased respiratory muscle work. On the other hand, breathing at high lung volumes requires marked increases in respiratory muscle work, which increases the patient's sensation of dyspnea[216]. Blunted ventilatory drive or a decrease in the perception of dyspnea in bronchial asthma and chronic obstructive pulmonary disease (COPD) could lead to a decrease in the alarm reaction to dangerous situations such as severe airway obstruction, severe hypoxemia, or severe hypercapnia[214] (and consequently blood acidification). Metabolic acidosis is a common finding in acute severe asthma, and suggest that the pathogenesis of lactic acidosis is multifactorial and includes contributions from lactate production by respiratory muscles, tissue hypoxia, and intracellular alkalosis[217]. The ventilatory drive to chemical stimuli can be altered by a beta-2-agonist, oxygen administration; and lung volume reduction and an increased dyspnea sensation may be improved by corticosteroid, chest wall vibration, or lung volume reduction. When hyperinflation is severe enough and persists long enough, the respiratory muscles may fatigue. In asthma, fatigue is likely accelerated by hypercapnia (if present), hypoxemia and reduced blood flow in muscles that are working at a mechanical disadvantage when shortened to below their optimal length by thoracic overinflation[218,219]. Physical signs of respiratory muscle fatigue are easily elicited: the respiratory rate increases, alternation between abdominal and rib cage breathing (respiratory alternans) occurs, and paradoxical diaphragmatic movement can be detected by palpation over the upper part of the abdomen[220]. These physical signs may precede the development of overt respiratory failure and give warning of impending respiratory arrest.

Aside from hyperinflation, another important consequence of airway inflammation in asthma is modification of the ventilatory drive. Patients suffering from asthma can develop different acid base disturbances, where a low partial pressure of carbon dioxide (pCO_2) is far more common than a high pCO_2, even in the presence of severe airways obstruction[215,221].

A study examined the clinical features, arterial blood gases, and acid-base profile in 229 consecutive episodes of acute asthma in 170 patients who required hospitalization[217]. A simple respiratory alkalosis was the most common acid-base disturbance, occurring in 48 percent of the episodes. Metabolic acidosis, either alone or as part of a mixed disturbance, was noted in 28 percent of them. Of 60 episodes presenting with respiratory acidosis, 37 (62 percent) had a coexistent metabolic acidosis. Most episodes of asthma are characterized by alveolar hyperventilation and intense dyspnea; hypoventilation along with hypercapnia occurs so rarely that it is regarded by the clinician as a grave prognostic sign[215].

Relationship between asthma and anxiety disorders

From our results we might elucidate that changes in the breathing patterns on patients suffering from asthma and anxiety could be a key factor in the development of a determinate acid base status, including the effect of medication. In our study subjects a predominant alkaline status is associated with the use of drugs for obstructive airway diseases and anxiolytics. The relationship between asthma and anxiety is well-established. Symptoms, such as respiratory discomfort, are highly common in both panic disorder and in asthma. Previous cross-sectional community-based studies have provided evidence for a relatively specific association between the prevalence of asthma and panic disorder[222,223]. Chronic hyperventilation is probably a precondition of (respiratory subtype) panic attack[202]. Both anxiety and depression are known to influence the quality of life in asthmatics, and both put stress on the health care system[224]. A previous longitudinal study showed that asthma increases the risk of panic, anxiety, and depression[223]. More complex models have described asthma as an organic disease that is highly vulnerable to psychological influences[225,226].

Mood disorders were identified in 53% of asthmatic patients and in 34.9% of non-asthmatics[227]. There is evidence that breathing retraining improves the clinical control of asthma symptoms, anxiety symptoms, and the health-related quality of life in asthmatics[228].

Since the introduction of medical therapy for asthma the interest in non-medical treatments has been deteriorated. Physiotherapy could have beneficial effects in asthmatics. A recent study investigates the effectiveness of physiotherapy in the treatment of patients with asthma[229]. A review was performed on the terms breathing exercises (BE), inspiratory muscle training (IMT), physical training (PhT) and airway clearance (AC) in patients with asthma. They concluded that BE may improve disease specific quality of life; reduce symptoms, hyperventilation, anxiety and depression, lower respiratory rate and medication use. IMT can improve inspiratory pressure and may reduce medication use and symptoms. PhT can reduce symptoms, improve quality of life and improve cardiopulmonary endurance and fitness.

STRENGTHS

Data collection for this report has been taken from a case-control study on bladder cancer. The association between medications with the generation of acidic or non-acidic urine pH has been performed on control subjects of the case-control study to increase internal and external validity. The control group is probably unbiased as the case control study has confirmed all the associations that were expected.

To date, this is the first study on medication use and its influence on urine pH in humans.

A single pH measurement from a regular AM spot urine sample cannot be used to identify individuals with constantly acidic pH[230]. In a previous study we showed that only 25% of the subjects with an acidic AM spot urine sample from a given day had acidic levels throughout a week, and that to capture day-to-day urine pH variability, measuring urine pH with pH strips twice a day (first void in the morning and early in the evening) during four consecutive days classified most people in the same way as recording measurements during six and a half consecutive days[230].

Dietary factors like vegetable and fruit intake have been shown to influence urine pH in the literature. Some of the diseases (e.g., heart congestive disease and anxiety related disorders) for which the drugs studied are prescribed might influence the dietary intake of the patients. Hence, there was a potential for confounding due to dietary intake, which we have addressed by including daily grams of vegetables, daily grams of fruits and daily grams of meat intake in the multivariate models.

Adjustment for factors that could potentially influence urine pH, including height and weight[61,63], as well as for age, sex, study region, and vitamin C use, were taken into account on our results.

LIMITATIONS

However, some limitations of our study should also be mentioned. The possible impact of changes on medications while patients were hospitalized, treatment duration or a possible wide range of therapeutic doses used for the different patients on each medication, and incomplete/mistaken reporting were not taken into account in our analyses.

Also, the cross-sectional nature of the analyses demands caution with respect to assign causality to our findings. Both, pH measurements and drug intake information were recorded at the same time.

The average age of our study population was over 60, and the educational level was low, which may cause some errors in the pH measurements and drugs reporting. However, we believe that such bias would be independent of having acidic urine pH, and would be non-differential, and would tend to dilute the magnitude of the associations reported, but would not invalidate the associations reported.

We should be cautious in the interpretation of the associations based on low number of subjects, even if the associations were statistically significant. In these situations the statistical power of our analysis was low. Also, a small change in the number of subjects using a given medication might have an important impact on the risk estimators of the statistical model.

Another limitation relates to the high number of comparisons made in our study; thus, we cannot rule out that some of the associations were spurious or due to chance (i.e., false-positive associations).

IMPLICATIONS

Several biological processes developing changes in human pH homeostasis, like increases or decreases in respiratory ventilation, can be triggered by either medications, medical conditions the drugs are prescribed for, or/and the interaction between them in the course of disease . If the impact of these medications on urine pH is important we would expect to find associations between these medications and the diseases where urine pH might play an important causal role, as bladder cancer and kidney stones. And one could also observe confounded associations between the medical conditions the drugs are prescribed for, and diseases where urine pH is relevant.

Reviewing the role of pCO2 in different neuropsychiatric disorders looking to better understand the acid base balance expected on each disease, we think that the role of pCO2 could be a key factor to predict differences in acid base status of individuals suffering from anxiety disorders, though it is an important link between psyche and corpus. Under our point of view, current anxiety disorders treatment should add physiotherapy, education in stress recognition and the inclusion of stress-prevention habits (daily mild exercise, control of breathing, etc). Improving a chronic hyperventilation status may prevent or minimize the cascades of mechanism involved in the development of either hyper- or hypoarousal conditions and so to prevent progression of the anxiety disorder to either panic attacks or depression (also to dysthymia), and/or psychosomatic disorders.

Phenobarbital (PB), a barbiturate, is the most widely used anticonvulsant worldwide, and the oldest still commonly used. PB has also sedative and hypnotic properties but, as with other barbiturates, has been superseded by the benzodiazepines for these indications. Some studies have showed that PB was negatively associated with bladder cancer risk, proposing that PB use protects against bladder cancer by inducing enzymes that participate in the detoxification of human bladder carcinogens, such as the aminobiphenyls and naphthylamines, which are found in cigarette smoke[231,232]. In acidic urine pH conditions liver-

synthesized N-Glucuronides of aromatic amines from cigarette smoking excreted into the urinary bladder are rapidly hydrolyzed leading to the formation of their corresponding arylamines, which can then undergo further metabolism to form DNA adducts[127,128]. We suggest that PB use could be associated with the generation of non acidic urine pH and that this can be a key factor on its bladder cancer protection. Further studies should be done to assess PB use influence on urine pH levels. We did not analyze the association between PB and urine pH since there were too few subjects reporting PB intake among our study population.

Some publications have assessed the association between asthma, hay fever, or other allergy-related diseases and cancer that have reported a protective association for glioma, colorectal cancer, cancer of the larynx, non-Hodgkin lymphoma, cancer of the esophagus, oral cancer, pancreatic cancer, stomach cancer, and uterine body cancer; and an increased risk for bladder cancer, lymphoma, myeloma, and prostate cancer[233]. The suggested mechanisms to explain these associations are usually related to the immune system. However, for bladder cancer, we propose that a plausible mechanism would be the relationship between acute severe asthma exacerbation and acidic urine pH, which could be confounded by the use of medications to relieve obstructive airway diseases.

Also, in several studies N-acetylcysteine (NAC) has been described to be a way to prevent cystine and calcium oxalate renal stone formation (more easily formed in acidic urine) and recurrence[234], and also to be an alkaline agent used to dissolve cystine calculi[235]. In addition, NAC has been described to inhibit proliferation, adhesion, migration and invasion of human bladder cancer cells[236,237]. We did not analyze its association with urine pH since there were too few subjects reporting NAC intake among our study population. However, NAC is included in the ATC group of “cold and cough preparations”, which in our results showed a suggested association with not developing acidic urine among our study subjects. In the literature, we found recent studies suggesting that the protective effects of NAC (against kidney and lung injury) were attributable to the decrease in oxidative stress[238]. The effect of

NAC and other antioxidants in central carbon dioxide chemoreception, by augmenting the tidal volume, showed an increase in the sensitivity of the ventilatory response to carbon dioxide, either during unloaded breathing or after resistive breathing[239]. This improvement on the ventilatory response to carbon dioxide could be a relevant factor in the proved protective role of NAC in kidney stones and bladder cancer. This protection is mediated by preventing the acidification of blood and consequently of urine in subjects suffering a hypoventilation status (decreased excretion of CO_2) from lung diseases or other causes.

Further studies are warranted for a better understanding on how medications involved in biological processes changing pH homeostasis, and drug interaction with disease conditions, are associated with urine pH levels. Identification of the generation of constantly acidic urine pH in subjects taking some medications could enhance to improve treatments and prophylaxis in patients with bladder cancer, kidney stones and other diseases, including dietary counselling.

Future lines of research could include reproduction of our study results in another study population to check the accordance with the associations found on our results. More specific study designs to explore the associations between medication use and urine pH in medical conditions as anxiety disorders, cardiac conditions or COPD (including asthma), could be also relevant to support our findings.

It could be also interesting to explore the associations between medication use and medical conditions/diseases where urine pH had been reported or suggested to influence on its development (i.e., bladder cancer, kidney stones or osteoporosis); or to study the associations between these pH influenced conditions/diseases mentioned above and anxiety disorders, cardiac conditions or COPD (including asthma) suggested on our conclusions to possibly influence in the generation or non-generation of constantly acidic urine pH.

7. Conclusions

7. CONCLUSIONS

1. The use of cardiac glycosides was found to have a significant association with having constantly acidic urine pH in our study population.

2. The use of drugs acting on respiratory system was found to have a significant association with not having constantly acidic urine pH in our study population.

3. The use of anxiolytics was found to have a significant association with not having constantly acidic urine pH in our study population.

4. The association between cardiac glycosides with having constantly acidic urine pH could be explained by both: the effect of the underlying cardiac diseases for which these drugs are prescribed for, and by the direct effect from such drugs on urine pH.

5. The association between anxiolytics with not having constantly acidic urine pH would most likely represents the effect of the hyperventilation generated from the underline anxiety disorder for which these drugs are prescribed, rather than a direct effect from such drugs on urine pH.

6. The association between drugs used in the respiratory system and not having constantly acidic urine pH could be explained by some states of chronic airway diseases, and by the direct effect from these drugs on urine pH.

8. Bibliography

8. BIBLIOGRAPHY

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9. Appendix

9. APPENDIX

Frequency of medications referred by the participants

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls).

Medication	Frequency	Percent (%)
ALIMENTARY TRACT AND METABOLISM (A)	1737	15,5
STOMATOLOGICAL PREPARATIONS (A01)	78	0,7
STOMATOLOGICAL PREPARATIONS (A01A)	78	0,7
DRUGS FOR ACID RELATED DISORDERS (A02)	882	7,9
ANTACIDS (A02A)	119	1,1
Magnesium carbonate (A02AA01)	10	0,1
Magnesium silicate (A02AA05)	18	0,2
Aluminium hydroxide (A02AB01)	16	0,1
Dihydroxialumini sodium carbonate (A02AB04)	16	0,1
Combinations and complexes of aluminium, calcium and magnesium compounds (A02AD)	63	0,6
Magaldrate (A02AD02)	6	0,1
Almagate (A02AD03)	47	0,4
Antacids with sodium bicarbonate (A02AH)	6	0,1
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE - GORD (A02B)	841	7,5
H2-receptor antagonists (A02BA)	391	3,5
Ranitidine (A02BA02)	315	2,8
Famotidine (A02BA03)	60	0,5
Prostaglandins (A02BB)	14	0,1
Misoprostol (A02BB01)	34	0,3
Proton pump inhibitors (A02BC)	432	3,8
Omeprazole (A02BC01)	248	2,2

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Pantoprazole (A02BC02)	38	0,3
Lansoprazole (A02BC03)	128	1,1
Silicones (A02D)	7	0,1
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS (A03)	117	1
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS (A03A)	83	0,7
Synthetic anticholinergics, esters with tertiary amino group (A03AA)	2	0
Trimebutine (A03AA05)	2	0
Dicycloverine (A03AA07)	47	0,4
Trospium (A03AB20)	23	0,2
Fenpiprane (A03AX01)	11	0,1
PROPULSIVES (A03F)	37	0,3
Propulsives (A03FA)	37	0,3
Metoclopramide (A03FA01)	10	0,1
Cisapride (A03FA02)	26	0,2
Clebopride (A03FA06)	1	0
BILE AND LIVER THERAPY (A05)	10	0,1
BILE THERAPY (A05A)	8	0,1
Other drugs for bile therapy (A05AX)	8	0,1
LIVER THERAPY, LIPOTROPICS (A05B)	2	0
Liver therapy (A05BA)	2	0
Silymarin (A05BA03)	2	0
DRUGS FOR CONSTIPATION (A06)	78	0,7
DRUGS FOR CONSTIPATION (A06A)	78	0,7
Contact laxatives (A06AB)	6	0,1
Bisacodyl (A06AB02)	6	0,1
Bulk-forming laxatives (A06AC)	31	0,3
Osmotically acting laxatives (A06AD)	47	0,4
Lactulose (A06AD11)	24	0,2
Lactitol (A06AD12)	21	0,2

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Sodium sulfate (A06AD13)	2	0
ANTIDIARRHEALS, INTESTINAL (A07) ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	22	0,2
ANTIPROPULSIVES (A07D)	14	0,1
Antipropulsives (A07DA)	14	0,1
Loperamide (A07DA03)	14	0,1
INTESTINAL ANTIINFLAMMATORY AGENTS (A07E)	8	0,1
Aminosalicylic acid and similar agents (A07EC)	8	0,1
Mesalazine (A07EC02)	8	0,1
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS (A08)	6	0,1
ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS (A08A)	6	0,1
Peripherally acting antiobesity products (A08AB)	6	0,1
Orlistat (A08AB01)	6	0,1
DIGESTIVES, INCL. ENZYMES (A09)	75	0,7
DIGESTIVES, INCL. ENZYMES (A09A)	75	0,7
Enzyme preparations (A09AA)	11	0,1
Glutamic acid hydrochloride (A09AB01)	50	0,4
Citric acid (A09AB04)	14	0,1
DRUGS USED IN DIABETES (A10)	513	4,6
INSULINS AND ANALOGUES (A10A)	86	0,8
Insulin (human) (A10AB01)	8	0,1
Insulins and analogues for injection, intermediate-acting (A10AC)	54	0,5
Insulins and analogues for injection, intermediate-acting combined with fast-acting (A10AD)	40	0,4
Insulin (human) (A10AE01)	8	0,1
BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS (A10B)	435	3,9
Biguanides (A10BA)	49	0,4
Metformin (A10BA02)	49	0,4
Sulfonamides, urea derivatives (A10BB)	359	3,2
Glibenclamide (A10BB01)	250	2,2
Chlorpropamide (A10BB02)	16	0,1
Glipizide (A10BB07)	8	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Gliclazide (A10BB09)	46	0,4
Glimepiride (A10BB12)	47	0,4
Alpha glucosidase inhibitors (A10BF)	98	0,9
Acarbose (A10BF01)	88	0,8
Miglitol (A10BF02)	10	0,1
VITAMINS (A11)	237	2,1
VITAMINS (A11)	42	0,4
Vitamin A, plain (A11CA)	8	0,1
Retinol (vit A) (A11CA01)	10	0,1
Vitamin D and analogues (A11CC)	10	0,1
Calcitriol (A11CC04)	10	0,1
Colecalciferol (A11CC05)	22	0,2
VITAMIN B1, PLAIN AND IN COMBINATION WITH VITAMIN B6 AND B12 (A11D)	48	0,4
Vitamin B1, plain (A11DA)	8	0,1
Thiamine (vit B1) (A11DA01)	40	0,4
Sulbutiamine (A11DA02)	8	0,1
Vitamin B1 in combination with vitamin B6 and/or vitamin B12 (A11DB)	30	0,3
VITAMIN B-COMPLEX, INCL. COMBINATIONS (A11E)	4	0
Vitamin B-complex, plain (A11EA)	4	0
ASCORBIC ACID (VITAMIN C), INCL. COMBINATIONS (A11G)	74	0,7
Ascorbic acid (vit C) (A11GA01)	74	0,7
OTHER PLAIN VITAMIN PREPARATIONS (A11H)	111	1
Other plain vitamin preparations (A11HA)	12	0,1
Nicotinamide (A11HA01)	4	0
Nicotinamide (A11HA02)	101	0,9
Tocopherol (vit E) (A11HA03)	18	0,2
Riboflavin (vit B2) (A11HA04)	4	0
OTHER VITAMIN PRODUCTS, COMBINATIONS (A11J)	2	0
Combinations of vitamins (A11JA)	2	0
MINERAL SUPPLEMENTS (A12)	135	1,2

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
CALCIUM (A12A)	84	0,7
Calcium (A12AA)	34	0,3
Calcium glubionate (A12AA02)	2	0
Calcium carbonate (A12AA04)	66	0,6
Calcium, combinations with vitamin D and/or other drugs (A12AX)	22	0,2
POTASSIUM (A12B)	51	0,5
Potassium (A12BA)	35	0,3
Potassium chloride (A12BA01)	2	0
Potassium citrate (A12BA02)	14	0,1
Potassium hydrogencarbonate (A12BA04)	35	0,3
APPETITE STIMULANTS (A15)	2	0
APPETITE STIMULANTS (A15A)	2	0
APPETITE STIMULANTS (A15AA)	2	0
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS (A16)	2	0
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS (A16A)	2	0
Levocarnitine (A16AA01)	2	0
BLOOD AND BLOOD FORMING ORGANS (B)	933	8,3
ANTITHROMBOTIC AGENTS (B01)	762	6,8
ANTITHROMBOTIC AGENTS (B01A)	762	6,8
Vitamin K antagonists (B01AA)	168	1,5
Acenocoumarol (B01AA07)	168	1,5
Heparin group (B01AB)	213	1,9
Heparin (B01AB01)	4	0
Dalteparin (B01AB04)	41	0,4
Enoxaparin (B01AB05)	107	1
Nadroparin (B01AB06)	53	0,5
Sulodexide (B01AB11)	8	0,1
Platelet aggregation inhibitors excl. Heparin (B01AC)	356	3,2
Ditazole (B01AC01)	8	0,1
Clopidogrel (B01AC04)	44	0,4

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Ticlopidine (B01AC05)	83	0,7
Dipyridamole (B01AC07)	26	0,2
Triflusal (B01AC18)	121	1,1
Streptokinase (B01AD01)	33	0,3
ANTIHEMORRHAGICS (B02)	16	0,1
ANTIFIBRINOLYTICS (B02A)	8	0,1
Amino acids (B02AA)	8	0,1
Tranexamic acid (B02AA02)	8	0,1
VITAMIN K AND OTHER HEMOSTATICS (B02B)	8	0,1
Vitamin K (B02BA)	8	0,1
Phytomenadione (B02BA01)	8	0,1
ANTIANEMIC PREPARATIONS (B03)	136	1,2
IRON PREPARATIONS (B03A)	90	0,8
Iron bivalent, oral preparations (B03AA)	80	0,7
Ferrous fumarate (B03AA02)	6	0,1
Ferrous sulfate (B03AA07)	64	0,6
Iron trivalent, oral preparations (B03AB)	4	0
Iron in combination with folic acid (B03AD)	6	0,1
VITAMIN B12 AND FOLIC ACID (B03B)	58	0,5
Vitamin B12 (cyanocobalamin and analogues) (B03BA)	8	0,1
Cyanocobalamin (B03BA01)	22	0,2
Hydroxocobalamin (B03BA03)	26	0,2
Folic acid and derivatives (B03BB)	10	0,1
Folic acid (B03BB01)	16	0,1
OTHER ANTIANEMIC PREPARATIONS (B03X)	2	0
Other antianemic preparations (B03XA)	2	0
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS (B05)	26	0,2
IRRIGATING SOLUTIONS (B05C)	26	0,2
Sodium bicarbonate (B05CB04)	2	0
Glycine (B05CX03)	24	0,2

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
I.V. SOLUTION ADDITIVES (B05X)	2	0
Sodium phosphate (B05XA09)	2	0
OTHER HEMATOLOGICAL AGENTS (B06)	41	0,4
OTHER HEMATOLOGICAL AGENTS (B06A)	41	0,4
Enzymes (B06AA)	33	0,3
Chymotrypsin (B06AA04)	8	0,1
Trypsin (B06AA07)	8	0,1
CARDIOVASCULAR SYSTEM ©	2663	23,7
CARDIAC THERAPY (C01)	605	5,4
CARDIAC GLYCOSIDES (C01A)	269	2,4
Digitalis glycosides (C01AA)	143	1,3
Acetyldigoxin (C01AA02)	81	0,7
Digoxin (C01AA05)	143	1,3
ANTIARRHYTHMICS, CLASS I AND III (C01B)	71	0,6
Antiarrhythmics, class Ia (C01BA)	8	0,1
Quinidine (C01BA01)	8	0,1
Antiarrhythmics, class Ic (C01BC)	5	0
Propafenone (C01BC03)	5	0
Antiarrhythmics, class III (C01BD)	58	0,5
Amiodarone (C01BD01)	58	0,5
CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES (C01C)	7	0,1
Phenylephrine (C01CA06)	7	0,1
VASODILATORS USED IN CARDIAC DISEASES (C01D)	294	2,6
Organic nitrates (C01DA)	267	2,4
Glyceryl trinitrate (C01DA02)	118	1,1
Isosorbide dinitrate (C01DA08)	38	0,3
Isosorbide mononitrate (C01DA14)	105	0,9
Other vasodilators used in cardiac diseases (C01DX)	25	0,2
Molsidomine (C01DX12)	25	0,2

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
OTHER CARDIAC PREPARATIONS (C01E)	57	0,5
Prostaglandins (C01EA)	8	0,1
Other cardiac preparations (C01EB)	49	0,4
Trimetazidine (C01EB15)	49	0,4
ANTIHYPERTENSIVES (C02)	298	2,7
ANTIADRENERGIC AGENTS, CENTRALLY ACTING (C02A)	15	0,1
Reserpine (C02AA02)	8	0,1
Methyldopa (C02AB)	7	0,1
Methyldopa (levorotatory) (C02AB01)	7	0,1
Antiadrenergic agents, peripherally acting (C02C)	283	2,5
Alpha-adrenoreceptor antagonists (C02CA)	283	2,5
Prazosin (C02CA01)	6	0,1
Doxazosin (C02CA04)	277	2,5
ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION (C02L)	8	0,1
Rauwolfia alkaloids and diuretics in combination (C02LA)	8	0,1
DIURETICS (C03)	716	6,4
LOW-CEILING DIURETICS, THIAZIDES (C03A)	363	3,2
Thiazides, plain (C03AA)	64	0,6
Bendroflumethiazide (C03AA01)	4	0
Hydrochlorothiazide (C03AA03)	351	3,1
Thiazides, combinations with other drugs (C03AX)	8	0,1
LOW-CEILING DIURETICS, EXCL. THIAZIDES (C03B)	141	1,3
Sulfonamides, plain (C03BA)	114	1
Clopamide (C03BA03)	8	0,1
Chlortalidone (C03BA04)	59	0,5
Indapamide (C03BA11)	74	0,7
HIGH-CEILING DIURETICS (C03C)	200	1,8
Sulfonamides, plain (C03CA)	178	1,6
Furosemide (C03CA01)	106	0,9
Torasemide (C03CA04)	94	0,8

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
POTASSIUM-SPARING AGENTS (C03D)	154	1,4
Aldosterone antagonists (C03DA)	16	0,1
Spironolactone (C03DA01)	28	0,2
Amiloride (C03DB01)	104	0,9
Triamterene (C03DB02)	22	0,2
DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION (C03E)	138	1,2
Low-ceiling diuretics and potassium-sparing agents (C03EA)	116	1
Altizide and potassium-sparing agents (C03EA04)	12	0,1
High-ceiling diuretics and potassium-sparing agents (C03EB)	22	0,2
PERIPHERAL VASODILATORS (C04)	223	2
PERIPHERAL VASODILATORS (C04A)	223	2
Purine derivatives (C04AD)	127	1,1
Pentoxifylline (C04AD03)	127	1,1
Ergot alkaloids (C04AE)	40	0,4
Nicergoline (C04AE02)	8	0,1
Dihydroergocristine (C04AE04)	32	0,3
Other peripheral vasodilators (C04AX)	64	0,6
Vinburnine (C04AX17)	8	0,1
Buflomedil (C04AX20)	48	0,4
Naftidrofuryl (C04AX21)	8	0,1
VASOPROTECTIVES (C05)	134	1,2
AGENTS FOR TREATMENT OF HEMORRHOIDS AND ANAL FISSURES FOR TOPICAL USE (C05A)	8	0,1
Corticosteroids (C05AA)	8	0,1
ANTIVARICOSE THERAPY (C05B)	31	0,3
Heparins or heparinoids for topical use (C05BA)	8	0,1
Other sclerosing agents (C05BX)	23	0,2
Calcium dobesilate (C05BX01)	23	0,2
CAPILLARY STABILIZING AGENTS (C05C)	95	0,8
Bioflavonoids (C05CA)	47	0,4
Diosmin (C05CA03)	8	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Troxerutin (C05CA04)	39	0,3
Other capillary stabilizing agents (C05CX)	48	0,4
BETA BLOCKING AGENTS (C07)	410	3,7
BETA BLOCKING AGENTS (C07A)	410	3,7
Beta blocking agents, non-selective (C07AA)	71	0,6
Oxprenolol (C07AA02)	8	0,1
Propranolol (C07AA05)	63	0,6
Beta blocking agents, selective (C07AB)	282	2,5
Metoprolol (C07AB02)	19	0,2
Atenolol (C07AB03)	205	1,8
Bisoprolol (C07AB07)	89	0,8
Alpha and beta blocking agents (C07AG)	26	0,2
Carvedilol (C07AG02)	26	0,2
BETA BLOCKING AGENTS AND THIAZIDES C07B	4	0
Beta blocking agents, selective, and thiazides (C07BB)	4	0
BETA BLOCKING AGENTS AND OTHER DIURETICS (C07C)	19	0,2
Beta blocking agents, selective, and other diuretics (C07CB)	19	0,2
BETA BLOCKING AGENTS AND OTHER ANTIHYPERTENSIVES (C07F)	8	0,1
Beta blocking agents, selective, and other antihypertensives (C07FB)	8	0,1
CALCIUM CHANNEL BLOCKERS (C08)	845	7,5
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS (C08C)	541	4,8
Dihydropyridine derivatives (C08CA)	533	4,7
Amlodipine (C08CA01)	126	1,1
Felodipine (C08CA02)	40	0,4
Nicardipine (C08CA04)	12	0,1
Nifedipine (C08CA05)	226	2
Nimodipine (C08CA06)	71	0,6
Nisoldipine (C08CA07)	10	0,1
Nitrendipine (C08CA08)	24	0,2
Lacidipine (C08CA09)	16	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Lercanidipine (C08CA13)	18	0,2
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS (C08D)	320	2,8
Phenylalkylamine derivatives (C08DA)	72	0,6
Verapamil (C08DA01)	104	0,9
Benzothiazepine derivatives (C08DB)	216	1,9
Diltiazem (C08DB01)	216	1,9
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM (C09)	950	8,5
ACE INHIBITORS, PLAIN (C09A)	784	7
ACE inhibitors, plain (C09AA)	585	5,2
Captopril (C09AA01)	117	1
Enalapril (C09AA02)	401	3,6
Lisinopril (C09AA03)	62	0,6
Perindopril (C09AA04)	22	0,2
Ramipril (C09AA05)	20	0,2
Quinapril (C09AA06)	54	0,5
Cilazapril (C09AA08)	60	0,5
Fosinopril (C09AA09)	16	0,1
Trandolapril (C09AA10)	40	0,4
ACE INHIBITORS, COMBINATIONS (C09B)	207	1,8
ACE inhibitors and diuretics (C09BA)	175	1,6
ACE inhibitors and calcium channel blockers (C09BB)	32	0,3
ANGIOTENSIN II ANTAGONISTS, PLAIN (C09C)	166	1,5
Angiotensin II antagonists, plain (C09CA)	158	1,4
Losartan (C09CA01)	48	0,4
Valsartan (C09CA03)	21	0,2
Irbesartan (C09CA04)	40	0,4
Candesartan (C09CA06)	25	0,2
Telmisartan (C09CA07)	32	0,3
ANGIOTENSIN II ANTAGONISTS, COMBINATIONS (C09D)	8	0,1
Angiotensin II antagonists and diuretics C09DA	8	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
LIPID MODIFYING AGENTS (C10)	568	5,1
LIPID MODIFYING AGENTS, PLAIN (C10A)	568	5,1
HMG CoA reductase inhibitors (C10AA)	468	4,2
Simvastatin (C10AA01)	120	1,1
Pravastatin (C10AA03)	72	0,6
Fluvastatin (C10AA04)	8	0,1
Atorvastatin (C10AA05)	142	1,3
Cerivastatin (C10AA06)	45	0,4
Fibrates(C10AB)	108	1
Bezafibrate (C10AB02)	47	0,4
Fenofibrate (C10AB05)	16	0,1
Other lipid modifying agents (C10AX)	8	0,1
DERMATOLOGICALS (D)	24	0,2
PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS (D03)	4	0
CICATRIZANTS (D03A)	4	0
Dexpanthenol (D03AX03)	4	0
ANTIPSORIATICS (D05)	8	0,1
ANTIPSORIATICS FOR SYSTEMIC USE (D05B)	8	0,1
Other antipsoriatics for systemic use (D05BX)	8	0,1
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE (D06)	12	0,1
ANTIBIOTICS FOR TOPICAL USE (D06A)	12	0,1
Tyrothricin (D06AX08)	4	0
CHEMOTHERAPEUTICS FOR TOPICAL USE (D06B)	8	0,1
Lysozyme (D06BB07)	8	0,1
GENITO URINARY SYSTEM AND SEX HORMONES (G)	687	6,1
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03)	26	0,2
HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE (G03A)	24	0,2
Megestrol (G03AC05)	8	0,1
Medroxyprogesterone (G03AC06)	16	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
OTHER SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM (G03X)	2	0
Selective estrogen receptor modulators (G03XC)	2	0
Raloxifene (G03XC01)	2	0
UROLOGICALS (G04)	661	5,9
UROLOGICALS (G04B)	134	1,2
Urinary concrement solvents (G04BC)	14	0,1
Drugs for urinary frequency and incontinence (G04BD)	120	1,1
Flavoxate (G04BD02)	46	0,4
Oxybutynin (G04BD04)	23	0,2
Tolterodine (G04BD07)	28	0,2
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY (G04C)	528	4,7
Alpha-adrenoreceptor antagonists (G04CA)	320	2,8
Alfuzosin (G04CA01)	28	0,2
Tamsulosin (G04CA02)	216	1,9
Terazosin (G04CA03)	76	0,7
Testosterone-5-alpha reductase inhibitors (G04CB)	82	0,7
Finasteride (G04CB01)	82	0,7
Other drugs used in benign prostatic hypertrophy (G04CX)	134	1,2
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS (H)	237	2,1
CORTICOSTEROIDS FOR SYSTEMIC USE (H02)	179	1,6
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN (H02A)	179	1,6
Glucocorticoids (H02AB)	86	0,8
Dexamethasone (H02AB02)	6	0,1
Prednisone (H02AB07)	22	0,2
Deflazacort (H02AB13)	46	0,4
Budesonide (H02AB16)	89	0,8
CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS (H02B)	4	0
Corticosteroids for systemic use, combinations (H02BX)	4	0

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
THYROID THERAPY (H03)	50	0,4
THYROID PREPARATIONS (H03A)	42	0,4
Thyroid hormones (H03AA)	42	0,4
Levothyroxine sodium (H03AA01)	42	0,4
ANTITHYROID PREPARATIONS (H03B)	8	0,1
Sulfur-containing imidazole derivatives (H03BB)	8	0,1
Thiamazole (H03BB02)	8	0,1
CALCIUM HOMEOSTASIS (H05)	8	0,1
ANTI-PARATHYROID AGENTS (H05B)	8	0,1
Calcitonin preparations (H05BA)	8	0,1
Calcitonin (human synthetic) (H05BA03)	8	0,1
ANTIINFECTIVES FOR SYSTEMIC USE (J)	915	8,1
ANTIBACTERIALS FOR SYSTEMIC USE (J01)	901	8
TETRACYCLINES (J01A)	2	0
Tetracyclines (J01AA)	2	0
Doxycycline (J01AA02)	2	0
BETA-LACTAM ANTIBACTERIALS, PENICILLINS (J01C)	129	1,1
Penicillins with extended spectrum (J01CA)	44	0,4
Amoxicillin (J01CA04)	119	1,1
Beta-lactamase resistant penicillins (J01CF)	10	0,1
Cloxacillin (J01CF02)	10	0,1
Amoxicillin and enzyme inhibitor (J01CR02)	75	0,7
OTHER BETA-LACTAM ANTIBACTERIALS (J01D)	76	0,7
Cephalosporins (J01DA)	76	0,7
SULFONAMIDES AND TRIMETHOPRIM (J01E)	7	0,1
Sulfamethoxazole and trimethoprim (J01EE01)	7	0,1
MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS (J01F)	32	0,3

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Macrolides (J01FA)	30	0,3
Erythromycin (J01FA01)	2	0
Spiramycin (J01FA02)	2	0
Roxithromycin (J01FA06)	12	0,1
Clarithromycin (J01FA09)	8	0,1
Azithromycin (J01FA10)	8	0,1
AMINOGLYCOSIDE ANTIBACTERIALS (J01G)	8	0,1
Other aminoglycosides (J01GB)	8	0,1
Gentamicin (J01GB03)	8	0,1
QUINOLONE ANTIBACTERIALS (J01M)	634	5,6
Ofloxacin (J01MA01)	56	0,5
Ciprofloxacin (J01MA02)	455	4,1
Norfloxacin (J01MA06)	111	1
Pipemidic acid (J01MB04)	12	0,1
COMBINATIONS OF ANTIBACTERIALS (J01R)	2	0
Combinations of antibacterials (J01RA)	2	0
OTHER ANTIBACTERIALS (J01X)	27	0,2
Metronidazole (J01XD01)	18	0,2
Jinidazole (J01XD02)	8	0,1
Other antibacterials (J01XX)	1	0
Fosfomycin (J01XX01)	1	0
ANTIMYCOTICS FOR SYSTEMIC USE (J02)	8	0,1
ANTIMYCOTICS FOR SYSTEMIC USE (J02A)	8	0,1
Triazole derivatives (J02AC)	8	0,1
Fluconazole (J02AC01)	8	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
ANTIMYCOBACTERIALS (J04)	2	0
DRUGS FOR TREATMENT OF TUBERCULOSIS (J04A)	2	0
Hydrazides (J04AC)	2	0
Isoniazid (J04AC01)	2	0
ANTIVIRALS FOR SYSTEMIC USE (J05)	4	0
DIRECT ACTING ANTIVIRALS (J05A)	4	0
Nucleosides and nucleotides excl. reverse transcriptase inhibitors (J05AB)	4	0
Aciclovir (J05AB01)	4	0
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS (L)	146	1,3
ANTINEOPLASTIC AGENTS (L01)	20	0,2
ANTIMETABOLITES (L01B)	2	0
Folic acid analogues (L01BA)	2	0
Methotrexate (L01BA01)	2	0
CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES (L01D)	2	0
Other cytotoxic antibiotics (L01DC)	2	0
Mitomycin (L01DC03)	2	0
OTHER ANTINEOPLASTIC AGENTS (L01X)	16	0,1
Other antineoplastic agents (L01XX)	16	0,1
Hydroxycarbamide (L01XX05)	16	0,1
ENDOCRINE THERAPY (L02)	96	0,9
HORMONES AND RELATED AGENTS (L02A)	26	0,2
HORMONE ANTAGONISTS AND RELATED AGENTS (L02B)	24	0,2
Gonadotropin releasing hormone analogues (L02AE)	2	0
Triptorelin (L02AE04)	2	0
HORMONE ANTAGONISTS AND RELATED AGENTS (L02B)	70	0,6
Anti-estrogens (L02BA)	7	0,1
Tamoxifen (L02BA01)	7	0,1
Anti-androgens (L02BB)	63	0,6

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Flutamide (L02BB01)	18	0,2
Bicalutamide (L02BB03)	45	0,4
IMMUNOSUPPRESSANTS (L04)	30	0,3
IMMUNOSUPPRESSANTS (L04A)	30	0,3
Selective immunosuppressants (L04AA)	16	0,1
Ciclosporine (L04AA01)	16	0,1
Other immunosuppressants (L04AX)	14	0,1
Azathioprine (L04AX01)	14	0,1
MUSCULO-SKELETAL SYSTEM (M)	664	5,9
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS (M01)	446	4
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS (M01A)	446	4
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS (M01A)	6	0,1
Phenylbutazone (M01AA01)	6	0,1
Acetic acid derivatives and related substances (M01AB)	274	2,4
Indometacin (M01AB01)	14	0,1
Diclofenac (M01AB05)	166	1,5
Ketorolac (M01AB15)	16	0,1
Aceclofenac (M01AB16)	78	0,7
Oxicams (M01AC)	56	0,5
Meloxicam (M01AC06)	46	0,4
Propionic acid derivatives (M01AE)	78	0,7
Ibuprofen (M01AE01)	55	0,5
Naproxen (M01AE02)	13	0,1
Ketoprofen (M01AE03)	10	0,1
Coxibs (M01AH)	6	0,1
Celecoxib (M01AH01)	6	0,1
Other antiinflammatory and antirheumatic agents, non-steroids (M01AX)	18	0,2
Nabumetone (M01AX01)	8	0,1
Glucosamine (M01AX05)	10	0,1
Benzydamine (M01AX07)	8	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN (M02)	18	0,2
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN (M02A)	18	0,2
Piroxicam (M02AA07)	10	0,1
Capsaicin and similar agents (M02AB)	8	0,1
MUSCLE RELAXANTS (M03)	37	0,3
MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS (M03B)	37	0,3
Other centrally acting agents (M03BX)	37	0,3
Baclofen (M03BX01)	6	0,1
Tizanidine (M03BX02)	11	0,1
Tetrazepam (M03BX07)	12	0,1
Cyclobenzaprine (M03BX08)	8	0,1
ANTIGOUT PREPARATIONS (M04)	202	1,8
ANTIGOUT PREPARATIONS (M04A)	202	1,8
Preparations inhibiting uric acid production (M04AA)	171	1,5
Allopurinol (M04AA01)	171	1,5
Preparations with no effect on uric acid metabolism (M04AC)	47	0,4
Colchicine (M04AC01)	47	0,4
DRUGS FOR TREATMENT OF BONE DISEASES (M05)	14	0,1
DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION (M05B)	14	0,1
Bisphosphonates (M05BA)	14	0,1
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM (M09)	2	0
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM (M09A)	2	0
Other drugs for disorders of the musculo-skeletal system (M09AX)	2	0
NERVOUS SYSTEM (N)	1898	16,9
ANESTHETICS (N01)	8	0,1
ANESTHETICS, LOCAL (N01B)	8	0,1
Capsaicin (N01BX04)	8	0,1
ANALGESICS (N02)	1120	10
OPIOIDS (N02A)	42	0,4
Other opioids (N02AX)	42	0,4

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Tramadol (N02AX02)	42	0,4
OTHER ANALGESICS AND ANTIPYRETICS (N02B)	1070	9,5
Salicylic acid and derivatives (N02BA)	463	4,1
Acetylsalicylic acid (N02BA01)	547	4,9
Pyrazolones (N02BB)	292	2,6
Metamizole sodium (N02BB02)	292	2,6
Propyphenazone (N02BB04)	2	0
Anilides (N02BE)	273	2,4
Paracetamol (N02BE01)	273	2,4
ANTIMIGRAINE PREPARATIONS (N02C)	18	0,2
Ergot alkaloids (N02CA)	10	0,1
Dihydroergotamine (N02CA01)	10	0,1
Ergotamine (N02CA02)	8	0,1
ANTIEPILEPTICS (N03)	118	1,1
ANTIEPILEPTICS (N03A)	118	1,1
Barbiturates and derivatives (N03AA)	24	0,2
Phenobarbital (N03AA02)	32	0,3
Hydantoin derivatives (N03AB)	20	0,2
Phenytoin (N03AB02)	20	0,2
Benzodiazepine derivatives (N03AE)	14	0,1
Clonazepam (N03AE01)	14	0,1
Carboxamide derivatives (N03AF)	40	0,4
Carbamazepine (N03AF01)	40	0,4
Fatty acid derivatives (N03AG)	6	0,1
Valpromide (N03AG02)	6	0,1
Other antiepileptics (N03AX)	16	0,1
Gabapentin (N03AX12)	16	0,1
ANTI-PARKINSON DRUGS (N04)	32	0,3
DOPAMINERGIC AGENTS (N04B)	32	0,3
Dopa and dopa derivatives (N04BA)	16	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Levodopa (N04BA01)	16	0,1
Monoamine oxidase B inhibitors (N04BD)	16	0,1
Selegiline (N04BD01)	16	0,1
Other dopaminergic agents (N04BX)	8	0,1
Entacapone (N04BX02)	8	0,1
PSYCHOLEPTICS (N05)	702	6,3
ANTIPSYCHOTICS (N05A)	64	0,6
Benzamides (N05AL)	24	0,2
Sulpiride (N05AL01)	52	0,5
Lithium (N05AN)	5	0
Lithium (N05AN01)	5	0
Other antipsychotics (N05AX)	7	0,1
Risperidone (N05AX08)	7	0,1
ANXIOLYTICS (N05B)	586	5,2
Benzodiazepine derivatives (N05BA)	552	4,9
Diazepam (N05BA01)	109	1
Medazepam (N05BA03)	32	0,3
Potassium clorazepate (N05BA05)	80	0,7
Lorazepam (N05BA06)	162	1,4
Bromazepam (N05BA08)	84	0,7
Alprazolam (N05BA12)	92	0,8
Halazepam (N05BA13)	6	0,1
Clotiazepam (N05BA21)	10	0,1
Diphenylmethane derivatives (N05BB)	2	0
Hydroxyzine (N05BB01)	2	0
HYPNOTICS AND SEDATIVES (N05C)	134	1,2
Benzodiazepine derivatives (N05CD)	58	0,5
Flurazepam (N05CD01)	4	0
Lormetazepam (N05CD06)	30	0,3
Brotizolam (N05CD09)	8	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Loprazolam (N05CD11)	16	0,1
Benzodiazepine related drugs (N05CF)	45	0,4
Zopiclone (N05CF01)	14	0,1
Zolpidem (N05CF02)	31	0,3
Other hypnotics and sedatives (N05CM)	31	0,3
Clomethiazole (N05CM02)	15	0,1
Valerianae radix (N05CM09)	16	0,1
PSYCHOANALEPTICS (N06)	316	2,8
ANTIDEPRESSANTS (N06A)	222	2
Non-selective monoamine reuptake inhibitors (N06AA)	43	0,4
Clomipramine (N06AA04)	5	0
Amitriptyline (N06AA09)	70	0,6
Selective serotonin reuptake inhibitors (N06AB)	137	1,2
Fluoxetine (N06AB03)	27	0,2
Citalopram (N06AB04)	17	0,2
Paroxetine (N06AB05)	77	0,7
Sertraline (N06AB06)	8	0,1
Fluvoxamine (N06AB08)	8	0,1
Monoamine oxidase A inhibitors (N06AG)	8	0,1
Moclobemide (N06AG02)	8	0,1
Other antidepressants (N06AX)	18	0,2
Mianserin (N06AX03)	8	0,1
Mirtazapine (N06AX11)	8	0,1
Venlafaxine (N06AX16)	2	0
PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS (N06B)	76	0,7
Caffeine (N06BC01)	28	0,2
Other psychostimulants and nootropics (N06BX)	16	0,1
Piracetam (N06BX03)	40	0,4
Citicoline (N06BX06)	8	0,1
PSYCHOLEPTICS AND PSYCHOANALEPTICS IN COMBINATION (N06C)	32	0,3

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Antidepressants in combination with psycholeptics (N06CA)	32	0,3
ANTI-DEMENTIA DRUGS (N06D)	18	0,2
Anticholinesterases (N06DA)	2	0
Rivastigmine (N06DA03)	2	0
Other anti-dementia drugs (N06DX)	16	0,1
Ginkgo folium (N06DX02)	16	0,1
OTHER NERVOUS SYSTEM DRUGS (N07)	23	0,2
PARASYMPATHOMIMETICS (N07A)	8	0,1
Anticholinesterases (N07AA)	8	0,1
Pyridostigmine (N07AA02)	8	0,1
ANTIVERTIGO PREPARATIONS (N07C)	15	0,1
Antivertigo preparations (N07CA)	15	0,1
Betahistine (N07CA01)	15	0,1
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS (P)	14	0,1
ANTIPROTOZOALS (P01)	14	0,1
ANTIMALARIALS (P01B)	14	0,1
Aminoquinolines (P01BA)	14	0,1
Chloroquine (P01BA01)	14	0,1
RESPIRATORY SYSTEM (R)	507	4,5
NASAL PREPARATIONS (R01)	58	0,5
DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE (R01A)	56	0,5
Prednisolone (R01AD02)	8	0,1
Fluticasone (R01AD08)	48	0,4
NASAL DECONGESTANTS FOR SYSTEMIC USE (R01B)	2	0
Sympathomimetics (R01BA)	2	0
Phenylpropanolamine (R01BA01)	2	0
THROAT PREPARATIONS (R02)	12	0,1
THROAT PREPARATIONS (R02A)	12	0,1
Antiseptics (R02AA)	4	0
Antibiotics (R02AB)	8	0,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES (R03)	321	2,9
ADRENERGICS, INHALANTS (R03A)	206	1,8
Selective beta-2-adrenoreceptor agonists (R03AC)	104	0,9
Salbutamol (R03AC02)	120	1,1
Terbutaline (R03AC03)	8	0,1
Salmeterol (R03AC12)	64	0,6
Formoterol (R03AC13)	30	0,3
Adrenergics and other drugs for obstructive airway diseases (R03AK)	8	0,1
OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS (R03B)	171	1,5
Glucocorticoids (R03BA)	129	1,1
Beclometasone (R03BA01)	8	0,1
Anticholinergics (R03BB)	78	0,7
Ipratropium bromide (R03BB01)	78	0,7
ADRENERGICS FOR SYSTEMIC USE (R03C)	109	1
Selective beta-2-adrenoreceptor agonists (R03CC)	109	1
Terbutaline (R03CC03)	7	0,1
OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES (R03D)	116	1
Xanthines (R03DA)	116	1
Theophylline (R03DA04)	116	1
Leukotriene receptor antagonists (R03DC)	16	0,1
Zafirlukast (R03DC01)	8	0,1
Montelukast (R03DC03)	8	0,1
COUGH AND COLD PREPARATIONS (R05)	179	1,6
EXPECTORANTS, EXCL. COMBINATIONS WITH COUGH SUPPRESSANTS (R05C)	63	0,6
Mucolytics (R05CB)	61	0,5
Acetylcysteine (R05CB01)	26	0,2
Bromhexine (R05CB02)	2	0
Carbocisteine (R05CB03)	8	0,1
Ambroxol (R05CB06)	27	0,2
COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS (R05D)	124	1,1

Frequency distribution of medications reported by the Spanish Bladder Cancer Participants that measured their urine pH (cases and controls) (Cont´d)

Medication	Frequency	Percent (%)
Opium alkaloids and derivatives (R05DA)	53	0,5
Codeine (R05DA04)	83	0,7
Dextromethorphan (R05DA09)	29	0,3
Other cough suppressants (R05DB)	12	0,1
Cloperastine (R05DB21)	12	0,1
ANTIHISTAMINES FOR SYSTEMIC USE (R06)	44	0,4
ANTIHISTAMINES FOR SYSTEMIC USE (R06A)	44	0,4
Chlorphenamine (R06AB04)	26	0,2
Substituted ethylene diamines (R06AC)	7	0,1
Mepyramine (R06AC01)	7	0,1
Other antihistamines for systemic use (R06AX)	9	0,1
Cyproheptadine (R06AX02)	2	0
Ebastine (R06AX22)	9	0,1
SENSORY ORGANS (S)	22	0,2
OPHTHALMOLOGICALS (S01)	22	0,2
ANTIGLAUCOMA PREPARATIONS AND MIOTICS (S01E)	18	0,2
Beta blocking agents (S01ED)	18	0,2
Timolol (S01ED01)	10	0,1
Levobunolol (S01ED03)	8	0,1
Prostaglandin analogues (S01EE)	8	0,1
s01ex03	8	0,1
OTHER OPHTHALMOLOGICALS (S01X)	4	0
Other ophthalmologicals (S01XA)	2	0
Sodium chloride, hypertonic (S01XA03)	2	0
Mucolytics (R05CB)	61	0,5
Acetylcysteine (R05CB01)	26	0,2
Bromhexine (R05CB02)	2	0
Carbocisteine (R05CB03)	8	0,1
Ambroxol (R05CB06)	27	0,2
COUGH SUPPRESSANTS, EXCL. COMBINATIONS WITH EXPECTORANTS (R05D)	124	1,1