Mini-review

Metabolic syndrome and nephrolithiasis: can we hypotize a common background?

Giuseppe Mossetti[a]
Domenico Rendina[a,b]
Gianpaolo De Filippo[c]
Domenico Benvenuto[b]
Carmen Liliana Vivona[b]
Giorgia Zampa[a]
Pasquale Ferraro[b]
Pasquale Strazzullo[a]

[a] Department of Clinical and Experimental Medicine, Federico II University Medical School, Naples, Italy
[b] Spinelli Hospital, Belvedere Marittimo (CS), Italy
[c] Pediatric Endocrinology Unit, Gaetano Rummo Hospital, Benevento, Italy

Address for correspondence:
Giuseppe Mossetti, M.D.
Department of Clinical and Experimental Medicine,
Federico II University Medical School
Via S. Pansini 5, 80131 Naples, Italy
Ph. +39 081 7462017
Fax +39 081 5466152
E-mail: giumosse@unina.it

Summary

Metabolic syndrome and nephrolithiasis are quite common disorders presenting similar epidemiological characteristics. Belonging to genetic, environmental and hormonal interaction, they have high incidence and prevalence in the adult population of industrialised countries and are characterised by a high level of morbidity and mortality if not adequately identified and treated. Despite metabolic syndrome is considered a fundamental risk factor for chronic kidney diseases, is not actually known whether it is associated with nephrolithiasis beyond the effect of its individual components, in particular obesity, glucose intolerance, and hypertension. In this paper, the possible pathogenetic links between metabolic syndrome and nephrolithiasis will be presented and discussed.

KEY WORDS: metabolic syndrome, nephrolithiasis, insulin resistance, vitamin D, gender, dietary habits.

Introduction

In recent years, some scientific panels proposed to introduce the metabolic syndrome into clinical practice as a multidimensional risk condition for cardiovascular morbidity and mortality (1-5). Despite different definitions of metabolic syndrome have been proposed, there is general consensus regarding its main components: obesity, hypertension and disorders of carbohydrate and lipid metabolism [i.e., elevated serum triglyceride and apolipoprotein B (apoB), increased small LDL particles, and a reduced level of HDL cholesterol (HDL-C)]. Individuals with these characteristics commonly harbor a pro-inflammatory state, resulting in a pro-thrombotic condition. Along with many other chronic syndromes and diseases, metabolic syndrome belong to a multi-factorial origin and its pathogenesis can be classified into underlying causes and exacerbating factors (6, 7). The predominant underlying risk factors for the syndrome appear to be abdominal obesity and insulin-resistance. Other metabolic syndrome components could be considered exacerbating factors having a direct effect on atherosclerotic disease (6, 7). An atherogenic diet (e.g., a diet rich in saturated fat and cholesterol) can enhance risk for developing cardiovascular disease in people with the syndrome, although this diet is not listed specifically as an underlying risk factor for the condition (4). Physical inactivity, aging, and hormonal imbalance could be also considered as risk factors for the development of the metabolic syndrome (8-11). Screening programs for obesity and its complications would be justified if earlier intervention were shown to clearly reduce morbidity and mortality. Several systematic reviews have examined the evidence regarding the benefits, limitations and cost-effectiveness of a broad range of clinical preventive services for obesity.

Recent studies indicate metabolic syndrome as pivotal risk factor for chronic kidney diseases (12, 13). In the past few years, some of the metabolic syndrome components have been also associated with the occurrence of nephrolithiasis or with biochemical abnormalities which in turn are related to kidney stone disease (14-23), but is not actually known whether metabolic syndrome itself is associated with nephrolithiasis beyond the effect of its individual components. In this paper, the possible pathogenetic links between metabolic syndrome and nephrolithiasis will be discussed.

Epidemiology

Metabolic syndrome and nephrolithiasis present similar epidemiological characteristics. Both are caused by the interaction of genetic, environmental and hormonal factors, present a high incidence and prevalence in the adult population of industrialised countries and are characterised by a high level of morbidity and mortality if not adequately identified and treated (8, 10, 24). In particular, in Italy the prevalence of metabolic syndrome increases dramatically with age, from about 3% among people in their 20s to over 25% among people older than 70 years. Application of estimated prevalence data to the Italian adult population, suggests that more than 6 million individuals may have the metabolic syndrome, about 3.6 million women and 3 million men (25). On the other hand, at least 5% of Italians aged over 35 years of age have had a symptomatic episode of kidney stones, more than 100,000 admissions are recorded every year due to renal colic for an overall cost of over 200,000 million euro, and at least 3500 cases of chronic renal failure each year are secondary to nephrolithiasis (26). Finally, In the latter part of the 20th century both diseases showed an increased prevalence and incidence in adult women (27, 28).

Epidemiological preliminary data indicate that metabolic syn-

drome is a risk factor for nephrolithiasis in both gender. In this regard, in a hospital-based survey performed in Southern Italy, we found a significant association between metabolic syndrome and echographic evidence of nephrolithiasis (29).

Insulin-resistance and obesity

A first common pathogenetic background between metabolic syndrome and nephrolithiasis could be identified in the presence of insulin-resistance. As previously reported, insulin-resistance plays a crucial role in the initiation and maintenance of the various clinical features of metabolic syndrome (6, 7) and also significantly influences the urinary salts supersaturation (19, 30, 31). Kidney stone formation results from a phase change in which urinary dissolved salts condense into solids, and all phase changes are driven by salts supersaturation, which is usually approximated by the ratio of the urinary salt concentration to its solubility and is calculated by computer algorithms (24). In addition to urine volume, calcium and oxalate concentrations are the main determinants of calcium oxalate urine supersaturation. Urine calcium concentration and pH are the main determinants of calcium phosphate supersaturation and urinary pH is the main determinant of uric acid supersaturation (24). Insulin-resistance directly influences urinary salts supersaturation by affecting urinary pH as well as calcium, phosphate, urate and citrate excretion (19, 30, 31). A clinical condition tightly intertwined with insulin-resistance is obesity. Obesity causes insulin-resistance, and conversely, inherent forms of insulin-resistance modify adipose tissue responses to insulin and thereby recapitulate the obese state (6, 7, 32-34). Previous studies indicate that obesity was associated with greater risk of kidney stones disease (15, 22, 35, 36). Obesity and weight gain significantly influence calcium-oxalate and calcium-phosphate urine supersaturation acting on urinary pH as well as urinary calcium, phosphate and urate excretion (15, 22, 35, 36).

Vitamin D biological system, insulin-resistance and nephrolithiasis

Experimental studies also indicate the vitamin D biological system could play a role in the pathogenesis of both nephrolithiasis and insulin-resistance. Vitamin D endocrine system regulates multiple aspects of calcium and bone metabolism, including calcium absorption and excretion, but also plays an important role in glucose homeostasis, notably in the mechanism of insulin release (37-40). Vitamin D may have a beneficial effect on insulin action either directly, by stimulating the expression of insulin receptor, thereby enhancing insulin responsiveness for glucose transport (41), or indirectly via its role in regulating extracellular calcium ensuring normal calcium influx through cell membranes and adequate intracellular cytosolic ionized calcium pool (42, 43). Biological actions of vitamin D are mediated by the binding of $1,25(OH)_2D_3$ to a specific cytosolic/nuclear vitamin D receptor (VDR), a member of the steroid/thyroid hormone receptor superfamily and a vitamin D response elements (VDREs) has been detected in the human insulin receptor gene promoter (44-46).
Several frequent polymorphisms are found in the VDR gene and were reported to be associated with a variety of physiological and pathological phenotypes in many populations including the occurrence of insulin-resistance in diabetic type 2 patients as well as of idiopathic hypercalciuria and hypocitraturia in recurrent stone forming patients (47-54).

Influence of gender: the role of estrogen production

The magnitude of association between obesity and kidney stone disease varies by gender, with a stronger influence in women (21). The fall of estrogen production significantly influences the emergence of metabolic syndrome in postmenopausal women by increasing body mass index and visceral fat accumulation (11). On the other hand, ovarian failure significantly increases bone turnover and urinary calcium excretion and, at the same time, reduces the excretion of inhibitors of urinary crystal nucleation and growth (i.e., citrate) (55-57).
These data indicate that menopause and ovarian failure could be another pathogenic link between kidney stone disease and metabolic syndrome in women and could explain the increased prevalence of kidney stone disease observed in the last years in women (27, 28).

Dietary habits, metabolic syndrome, hypertension and nephrolithiasis

Changes in dietary habits and lifestyle contribute markedly to the rise in the prevalence and incidence of kidney stone disease as well as obesity, hypertension and metabolic syndrome (4, 58-60). The human diet before the Industrial Revolution was characterized by a large intake of fresh fruits and vegetables which guaranteed a large intake of potassium (100-200 mmol/day) (61). These foods rich in potassium were are also usually rich in HCO3-yielding precursors like citrate, and virtually no contain sodium. Conversely, the modern diet, which dates 200 years ago, is characterized by an higher content of sodium and chloride and a significantly lower content of potassium and HCO3-yielding substances (62). Indeed, the potassium/sodium and HCO3/chloride ratios have become reversed with the advent of the modern diet while the renal physiological properties remain largely unchanged, genetically fixed in Paleolithic time. Thus, the electrolytic mix of the modern diet is profoundly mismatched to its genetically determined processing machinery, and the extent of this diet-kidney mismatch increases with age, largely because the contemporary dietary intake of potassium decreases with age, as recently demonstrated in Caucasian-Americans and African-Americans cohorts (63). Renal sodium and calcium transports are close coupled and changes in tubular sodium handling directly affect urinary calcium excretion (64). In the kidney, sodium-dependent calcium reabsorption occurs in the proximal tubule, that is responsible for ~60% of calcium reabsorption by passive paracellular diffusion, and in the thick ascending loop. In the distal tubule, calcium reabsorption is primarily through the TRPV5 channel, expression of which is increased by parathyroid hormone and 1,25-dihydroxy vitamin D (65). Increased sodium intake increases urinary calcium excretion in humans; every increase of dietary sodium of 100 mmol (6 g of sodium chloride) causes an increase in urinary calcium excretion of 1 mmol (66, 67). This effect occurs in both calcium stone formers with hypercalciuria as well as in normal, non-stone forming adults (68, 69). Bicarbonate and organic anions such as citrate, but not chloride, mitigate the effect of increased dietary sodium intake increasing the urinary pH (70). Urinary alkalinization increase directly the renal calcium reabsorption and reduce also the calcium release from bone (71). Considering that an high dietary sodium is typical in obese patients, an increased sodium dietary intake is another possible link between kidney stone disease and metabolic syndrome (35, 70).
Diets rich in animal protein is considered an important determinant for occurrence of metabolic syndrome, but is also a risk factor for nephrolithiasis. In effect, this diet makes urine more

lithogenic by increasing uric acid and calcium excretion and decreasing citrate excretion and urinary pH (72-80). On the other hand, a statistical association between hypertension and nephrolithiasis in both cross-sectional and prospective epidemiological investigations has been reported by our group and by others (14, 16, 17, 81-83). As renal tubular calcium handling may be altered in hypertensive patients, leading to increased urinary calcium excretion (84), hypercalciuria seems a plausible pathogenetic link between the two conditions in subjects who carry genetic susceptibility and possibly other risk factors for nephrolithiasis (85).

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