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Review

An association between diet, metabolic syndrome and lower urinary tract symptoms

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Abstract
Diet is a key factor in the aetiology of many diseases, including metabolic syndrome and lower urinary tract disorders. Metabolic syndrome is a growing and increasingly expensive health problem in both the developed and the developing world, with an associated rise in morbidity and mortality. On the other hand, lower urinary tract symptoms affect millions of individuals worldwide, lowering their quality of life. Associations have been established between both conditions in existing literature and the various components of the metabolic syndrome have been linked with the onset and aggravation of symptoms in various forms of LUTS. This current review explores the relationships between these in detail, focusing on their inter-relationships particularly vis-a-vis dietary macronutrient and micronutrient intake.

Introduction

There is mounting evidence of environmental influences in the pathogenesis and course of many non-communicable diseases (NCDs). Diet, being one of the very key environmental factors, is capable of affecting health at the gross level, and at the genetic level through gene–nutrient interactions. Increasingly, diet is being recognised as playing a crucial role in the mechanisms involved in the pathophysiology and genetic predisposition, as well as the development and/or progression of diseases. This is due in large part to an increase in the consumption of 'western diets', which is being increasingly adopted by the developing societies.

Diet is the type of food, containing different nutrients in varying compositions, regularly consumed by an individual. The main macronutrients in diet are proteins, carbohydrates and fats, and these

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are varied in each diet according to choice, culture, health status, and economic strength of an individual. At the cellular level, these varying nutrients are absorbed and utilised for energy in the body through the body's metabolic processes [1]. Nutritionally poor diets have been linked to several chronic NCDs including metabolic syndrome (MetS) [2], a disorder which primarily originates from morbid obesity, often as a consequence of a high-fat diet. A 'balanced' diet is a diet which contains all of the individual macronutrients (and micronutrients) required for the optimal wellbeing and health of an individual. However, diets high in fats and carbohydrates are commonly consumed and these have been linked to several metabolic disorders.

MetS is an aggregation of disorders which include elevated triglycerides and apoprotein B – containing lipoproteins, reduced High Density Lipoprotein (HDL), arterial blood pressure elevation, and imbalances in glucose homeostasis with the main manifestations of this syndrome however being insulin resistance and abdominal obesity [3]. This syndrome is a global problem which has long posed a challenge to the developed world, and increasingly so to the developing societies of the world. Its incidence and prevalence is high in many countries amounting to a high socioeconomic cost, especially in costs of management of affected. MetS has been described as a major factor in the aetiology of lower urinary tract symptoms (LUTS) [3], increasing both predisposition to the disorder and the aggressiveness of the symptoms. Also, individual components of MetS have been reported to have strong associations with LUTS [4].

Lower urinary tract symptoms have been established as having a deleterious influence on quality of life for of adults irrespective of age, sex, and subpopulation [5]. The International Continence Society (ICS) has characterised LUTS into three classes which are storage, voiding, and post-micturition symptoms [6]. LUTS are often described in relation to benign prostatic hyperplasia (BPH) in men, especially those older than 60 years. However, LUTS could originate from other sources (see Fig. 1 below) [7] and the diet of an individual, especially elderly males, could be a predisposing factor. The commonest causes of LUTS include, (1) Diabetes mellitus

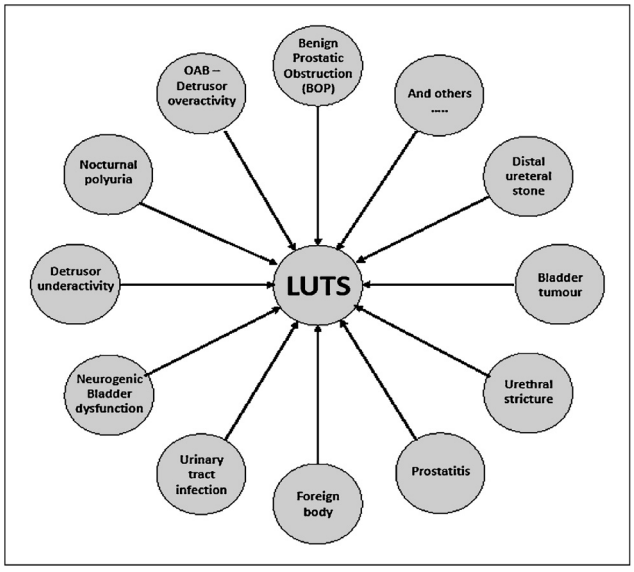

Fig. 1 European Association of Urology guidelines for factors causing LUTS [10].

(2) Overactive bladder which has been described as "a syndrome with urgency, with or without associated urine incontinence and usually accompanied by higher urinary frequency and nocturia" [8], and (3) Bladder Outlet Obstruction especially that secondary to benign prostatic hyperplasia which has a high prevalence, especially in older males. Despite the high prevalence of the latter two diseases, the mechanisms responsible for the voiding dysfunction are still a focus of intense research efforts.

Associations between metabolic syndrome and lower urinary tract symptoms

Type II diabetes mellitus has a strong association with moderate to severe LUTS. Besides being implicated in the origin of LUTS, DM has also been established as a deleterious factor in the more common LUTS, having an adverse effect on the bladder. More than half of patients have been established as demonstrating bladder abnormalities characterised by increased bladder capacity, weakened sensation, poor contractility, and increased postvoid residual urine [9]. Diabetic bladder dysfunction could be induced by diabetic neuropathy and/or the osmotic diuresis associated with diabetes mellitus [10,11]. Lee et al. reported that a high LUTS score might be a good marker for assessing diabetic bladder dysfunction [12].

Reduced testosterone concentrations are also associated with the metabolic syndrome. In the InCHIANTI study, the testosterone level was significantly reduced in elderly male participants with MetS [13]. A negative correlation was also reported for waist circumference and total testosterone in a study carried out in Argentina [14]. Decreased testosterone in MetS is attributable to the insulin resistance which results in hyperinsulinaemia. The increased insulin in circulation inhibits testosterone production by the Leydig cells [15]. Increase in adipocytokines is also another key factor responsible for low testosterone production. Leptin is a hormone secreted by fat cells which links food intake and energy expenditure to fat mass in the body and an increase in its secretion has been linked with low testosterone concentrations [16]. Also, of interest is the increase in aromatase activity linked with MetS. Adipocytes secrete aromatase which catalyses conversion of testosterone to estradiol, and its increased secretion in MetS, secondary to increased fat mass, results in a decrease in testosterone level. Low testosterone has been reported to have an inverse relationship to LUTS in men [17]. This interrelationship between MetS and LUTS could be adduced to microanatomical modifications which might result in loss of tissue elasticity and fibrosis which, eventually may correspond with the effect of testosterone on penile tissue in men with hypogonadism [18]

Insulin has been described as an independent risk factor for stimulation of prostatic hypertrophy in benign prostatic hyperplasia (BPH) [19]. Insulin resistance is one of the fundamental pathologies of MetS, which results in excessive insulin concentrations in blood (hyperinsulinaemia). Hyperinsulinaemia has been implicated as a factor in increased tone of prostatic smooth muscle [20]. This will eventually result in an increase in prostatic size and volume [21,22]. MetS progression results in chronic inflammation and this has been directly associated with prostate enlargement [23]. The inflammation process is characterised by increased T-lymphocytic activity, which in the prostate may give rise to proliferation of both stromal and epithelial cells, and this repetitive and continuous damage to the tissues followed by healing may eventually result in prostate

enlargement. Prostatic enlargement precipitates BPH which is a major cause of BOO, a key trigger of LUTS [3]. In the pathogenesis of MetS, insulin resistance has also been revealed as a cause of increased sympathetic activity [24]. Hyperinsulinaemia induces an increase in overall activity of the autonomic nervous system (ANS) which will result in prostatic hypertrophy as well as overactivity of the detrusor muscle. Stimulation of the α1-adrenoceptor has been implicated in dynamic obstruction, a mediation which is because of the associated increase in blood pressure [25]. Atherosclerosis in MetS results in narrowing of blood vessels predisposing them to chronic ischaemia. Pelvic ischaemia has been reported to decrease bladder compliance and contractile force while increasing void frequency in an animal model [26]. Narrowing of the blood vessels in atherosclerosis causes a drastic reduction in blood flow to the bladder during its filling. This processes of repeated ischaemia and subsequent reperfusion eventually stimulates high production of reactive oxygen species (ROS) which damages bladder tissues.

Serum C-Reactive Protein (CRP) level is considered a surrogate marker for chronic inflammation, a consideration which is synonymous to both metabolic syndrome and lower urinary tract symptoms, and elevated serum CRP levels have been linked with both conditions. CRP is produced by the liver in response to factors released by adipocytes and tissue macrophages, enhancing phagocytosis [27]. In patients enrolled in the Reduction by Dutasteride of Prostate Cancer Event study (REDUCE study), histology of the prostate showed chronic inflammation in 77.6% of men in prostatic biopsy specimens at baseline, revealing conclusive evidence of a relationship between the severity of LUTS and the degree of chronic inflammation [28]. A recent study has demonstrated a link between amount of CRP in serum and BPH and LUTS and that it rose with increase in age, PSA levels, as well as increased severity of LUTS, lower void volumes, and increases in storage symptoms [29]. Multivariate analysis also indicated that independent predictors associated with an elevated serum CRP level were IPSS and age, suggesting that increased serum CRP level can be associated with increased LUTS in men with BPH [30]. Studies into bladder pain syndrome or interstitial cystitis have also been providing increasing evidence which suggests that it is associated with urothelial dysfunction and afferent hyperexcitability due to neurogenic bladder inflammation [31]. Interestingly, high-sensitivity C-reactive protein (hs-CRP) level has been very beneficial in predicting the risk of cardiovascular disease and DM in asymptomatic people [32]. It is acknowledged as a very sensitive predictor of Type 2 diabetes mellitus and coronary heart disease and has been suggested for use as criteria for future definitions of metabolic syndrome [33]. Increase in serum CRP levels have an established association with MetS risk factors and has been shown to indicate a greater risk of cardiovascular disease [34].

Obesity, the precursor and predisposing factor to and a major component of MetS, has been described as being a strong risk factor for incontinence and LUTS and weight loss has been reported to reduce the frequency of urinary incontinence [35]. The reported outcomes of the Program to Reduce Incontinence by Diet and Exercise (PRIDE) clinical trial, showed that women who were overweight and obese presenting with urinary incontinence, when randomised to lifestyle intervention showed great improvement in urinary incontinence, especially for stress incontinence [36]. They described clinically and statistically significant reductions in urinary incontinent episodes with modest weight losses of 5–10%. In a different study based on analysis of data from the third National Health and Nutrition Examination Survey (NHANES III) and Healthy Eating Index (HEI), an association was reported between unhealthy diet consumption and LUTS after the investigators had controlled for other known modifiable risk factors [37]. This cross-sectional study carried out in the United States reported that a healthy diet (as defined by USDA HEI) was associated with lower self-reported LUTS in men over the age of 40 years. It however found no evidence to support a protective effect by any food group. They also reported evidence of higher self-reported LUTS in blacks and Hispanics. Other studies in this line include the Olmsted County study [38], the Flint study [39], the UrEpik study [40], the third National Health and Nutrition Examination Survey (NHANES) [41], the HUNT study [42], and the Boston Area Community Health (BACH) Survey [43]. Many of these studies reported significant associations between LUTS and factors like BMI (Body-Mass Index), Waist–Hip ratio, physical activity, diabetes mellitus as well as cardiovascular diseases (especially those affecting the heart). The BACH survey also reported a relationship between cardiovascular diseases and increased odds of LUTS and also that the effects of BMI and physical activity on the odds of LUTS were most prominent in women [43].

Diet, metabolic syndrome and lower urinary tract symptoms (LUTS)

All of the described origins of LUTS are influenced by macronutrient intake and these have been established in many studies [44,45]. Despite this, the extent of these relationships remains unclear and controversial. Results from some studies in surgically treated BPH assessing effects of macronutrients on LUTS were inconsistent [46], whilst another study established a positive relationship between total fat content of the body and BPH, while also reporting an inverse association between protein intake and BPH as defined by BPH treatment or a high protein score [47].

It was earlier reported that men who consumed diets high in energy content, especially those with high protein and polyunsaturated fatty acid (PUFA) content, had a higher predisposition to BPH [48]. The Prostate Cancer Prevention Trial (PCPT) results confirmed that high fat diets and high red meat consumption were associated with increase in the risk of Benign Prostatic Hyperplasia (BPH), while observing that high vegetable intake resulted in a reduction of the risk [49]. Several reports suggest that low fat/low energy diets, especially those containing large amounts of fruits and vegetables (rich in β-carotene lutein or vitamin C), which are well-known to protect against obesity and the resultant MetS, could also be protective against LUTS [49,50]. Lower incidences of BPH/LUTS and other prostate-related conditions have been observed in some Asian countries when compared with Western nations. This has been suggested to be related to the consumption of a mainly plant-based diet in those Asian countries whereas the Western diet is predominantly animal-based [51]. It is believed that high intake of unsaturated fatty acids might stimulate and worsen inflammation as well as impair 5α-reductase activity through a detrimental effect on the lipid membrane via its peroxidation [52]. Maserejian et al. described a high magnitude, dose-dependent association between high total energy intake and overall LUTS in women with low waist circumferences, and also reported that increased saturated fat intake was predictive of post-micturition symptoms [53]. Metabolic factors, as well as its associated lifestyle changes have been implicated in significantly increased risks of lower urinary tract symptoms. Associated dietary factors implicated include meat and high fat intake and it has been suggested that these might be viable considerations in the prevention and treatment of LUTS [54].

As earlier discussed, inflammation plays a major role in the aetiology of both MetS and LUTS. Dietary fatty acids can modulate markers of inflammation and consumption of high fat diets has been shown to increase concentrations of CRP [55]. Reports from the Harvard Women's Health Study showed a progressive increase in blood levels of hs-CRP with increasing glycemic index (GI). Dietary Glycemic Index (GI) is the mean propensity of carbohydrate in an individual's diet to increase blood glucose level [56]. Another study carried out in the Netherlands also showed the same trend [66]. Levels of saturated fatty acids (SFAs) in the diet have been positively correlated with hs-CRP [57] and a study in Indian youths revealed dietary saturated fatty acids (SFA) as the singularly most important nutrient responsible for increases in hs-CRP levels [58]. On the other hand, dietary polyunsaturated fatty acids (PUFA), and especially ω-3 PUFA, have been reported in several studies as having an inverse association with hs-CRP and other systemic markers of inflammation [59–61]. A review of experimental data reported that the acute inflammatory response to a single meal is influenced by the quantity and quality of dietary fat it contains. The authors concluded that SFA content is a major contributing factor to the magnitude of postprandial inflammatory response [62]. Carotenoids [63], flavonoids [64], magnesium [65], and fruits/vegetable consumption [66] have been reported to have an inverse association with hs-CRP.

As outlined above, insulin is another main factor implicated in both MetS and LUTS. Energy dense/high fat diets have a strong positive association with obesity and according to the World Health Organisation, are major contributors to overweight and obesity [67]. Obesity in turn is responsible for insulin insensitivity which is the major link among all MetS components and also causes prostatic enlargement. A high fat/high sucrose diet has been reported to reduce insulin sensitivity [68]. Maegawa et al. also observed that animals in a high sucrose group had highly elevated insulin levels, and this was also elevated in a different high-fat group [69]. High dietary fat intake is also a major influence on insulin action. Epidemiological and experimental evidence have linked high fat intake with insulin insensitivity/resistance [70] and the causative pathway for fat-induction of insulin resistance has been linked to Leptin activity in the body [71]. Leptin also has effects on adipocyte secretion [71] which in turn influences testosterone secretion [15].

Calcium has earlier been identified as having beneficial effects in management of body weight [72] via possible mechanisms of promoting lipolysis and inhibiting lipogenesis [73–75]. Reports suggest that in middle-aged males, introduction of calcium-channel blockers may be associated with increased severity of Lower Urinary Tract Symptoms [76]. These calcium-channel blockers are commonly used to treat a wide range of cardiovascular disorders but increased severity of LUTS was reported in the findings of Elhebir et al. Their results demonstrated that users of calcium antagonists had a higher likelihood of medical or surgical treatment for LUTS [77]. It can therefore be assumed that increases in calcium intake via diet could have a beneficial effect in individuals with both metabolic syndrome and LUTS, pointing to a possible relationship in the mechanisms for both.

Conclusion

The relationships between diet, metabolic syndrome and lower urinary tract symptoms are diverse and there are sundry mechanisms by which these associations occur. Serum CRP, insulin and testosterone, being common factors in both metabolic syndrome and lower urinary tract symptoms, attest to an association between the two. This lends even greater credence to a linkage between them; a linkage which could be exploited in deriving new therapies and investigations into these related conditions. Dietary interventions could be a mainline therapy for patients with metabolic syndrome exhibiting lower urinary tract symptoms but the extent of associations will have to be further investigated. Further research is required to clarify this relationship.

Authors' contribution

1. Temitope Gabriel Adedeji – Literature search, Concept plan formation, writing and editing of first and all subsequent manuscripts. 2. Adesoji A. Fasanmade – Concept plan formation, supervising of all editing of manuscripts. 3. Emiola O. Olapade-Olaopa – Concept plan formation, supervising of manuscript editing, editing of manuscripts.

Conflicts of interest

There are no conflicts of interest.

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