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Review

Cardio-metabolic and prostatic diseases in Nigeria: isn't what's good for the goose good for the gander?

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ABSTRACT: **Cardio-metabolic diseases prevalence is increasing globally and particularly in developing countries such as Nigeria. Socio-economic transformations in the affected regions have been blamed for the rising prevalence of these diseases. Prostatic diseases have also been shown to be as prevalent in Nigeria as they are in some developed countries, sparking worries of an impending 'outbreak' of morbid debility among the male population. Given the evidence, now available, of likely shared etiopathologic mechanisms linking both cardio-metabolic and prostatic diseases, it is worrisome that there exists a wide disparity in research output from Nigeria on both classes of diseases. This paper takes a cursory view of cardio-metabolic and prostatic diseases, examines the link between them, questions the yawning gap between them in terms of research output, and concludes that what's good for the goose should be good for the gander.**

KEYWORDS: **Cardio-metabolic diseases, prostatic diseases, etiopathologic mechanisms.**

Introduction

Cardio-metabolic diseases are increasing in prevalence globally and more so in developing countries such as Nigeria. This trend could be associated with the changing socio-economic environment in these regions, the rapid nutrition transitions and lifestyle changes, the increase in life expectancy, and the growing disposable income of a good proportion of the population. It appears from the aetiology of cardio-metabolic diseases, that hyperinsulinemia and visceral adiposity are the mechanisms linking and driving these diseases. Prostatic diseases, especially prostate cancer (PCa) and benign prostatic hyperplasia (BPH) constitute a good portion of the healthcare challenges of men globally. There is now evidence in the literature that the prevalence of these disorders are quite high even in developing countries such as Nigeria, where the sufferers are not spared the debility and loss of independence that come with the diseases. Interestingly, studies have shown that PCa and BPH may be linked in aetiology to the cardio-metabolic diseases, suggesting that prostatic diseases may be a continuation of the spectrum of disorders initiated by hyperinsulinemia and/or visceral adiposity.

What is worrisome is that whereas the rising prevalence of cardio-metabolic diseases in Nigeria has been matched with an increase in research activity (and possible funding) targeted at understanding such diseases and finding solutions to them, the same cannot be said of prostatic diseases. This paper therefore presents an over-view of the diseases and asks the question: isn't what's good for the goose (cardio-metabolic diseases) good for the gander (prostatic diseases)?

Cardio-metabolic diseases

Cardio-metabolic diseases refer to diseases of the cardiovascular system (disorders of the heart and the vasculature responsible for supplying blood to the central and peripheral tissues) and other diseases that result due to aberrations in the metabolic processes of an individual. They are often independent but inter-related, and result in severe debilitation, loss of independence, high mortality and socio-
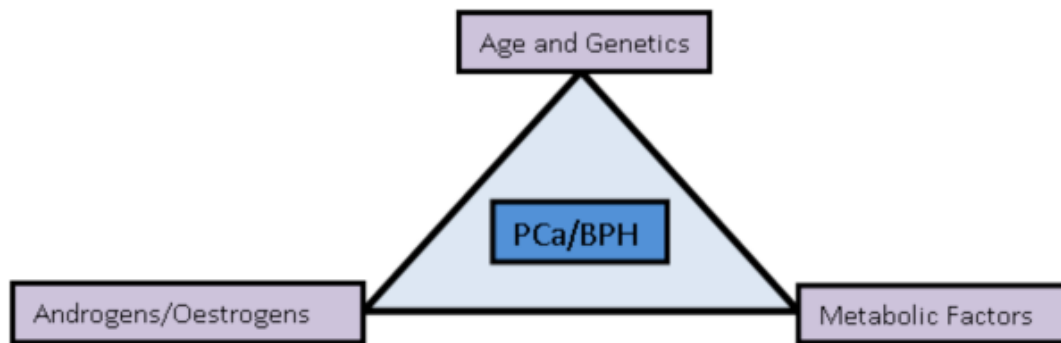
Figure 1: Triangular representation of the major etiopathologic factors involved in prostate cancer and BPH. PCa and BPH stand for prostate cancer and benign prostatic hyperplasia respectively.

economic losses. These diseases may be brought together under the umbrella of the metabolic syndrome, otherwise called syndrome X or insulin resistance syndrome (Asmar *et al.,* 2013). Components of this syndrome include obesity/visceral adiposity, insulin resistance and the attendant hyperinsulinemia, impaired glucose tolerance/type 2 diabetes mellitus, dyslipidemia (increased triacylglycerol, decreased high-density lipoprotein cholesterol (HDL-C), increased low-density lipoprotein cholesterol (LDL-C) and hypertension (Fan, 2007). The syndrome is diagnosed by the presence of visceral obesity [defined according to the International Diabetes Federation (IDF) as a waist circumference of ≥ 94 cm (men) or ≥ 80 cm (women) (for sub-Saharan Africans) (Grundy *et al.*, 2005)] and any other two of the following risk factors – elevated triacylglycerol [≥ 150 mg/dL (1.7 mmol/L)] or drug treatment for same; reduced HDL-C [< 40 mg/dL (1.0 mmol/L) in males; < 50 mg/dL (1.3 mmol/L) in females] or drug treatment for same; elevated blood pressure (systolic ≥ and/or diastolic ≥ 85 mmHg) or drug treatment for same; and elevated fasting blood glucose (≥ 100 mg/dL) or drug treatment for same; (i.e 3 out of 5 risk factors, provided visceral obesity is present) (Alberti *et al.*, 2005).

Cardio-metabolic diseases are quite prevalent. The WHO estimated that in 2008, over 500 million adults aged 20 years or more (200 million men and 300 million women) were obese while 1.4 billion were overweight (WHO, 2013). It is projected that by 2015, there will be approximately 700 million obese adults and 2.3 billion overweight ones. Regional variations abound, however such that whereas 1% or less of the Indian population is obese, as much as 80% of the population of some Pacific Islands are obese (Nguyen and El-Serag, 2010). The prevalence of overweight and obesity in Nigeria is put at 26.8% and 6.5% respectively (WHO 2011). Shaw *et al.* (2010) estimated that the prevalence of diabetes in adults will increase from 6.4% (285 million adults) in 2010 to 7.7% (439 million adults) in 2030. Strikingly, they estimate that the increase in the said period will amount to 69% in the developing countries and 20% in

developed countries. The IDF estimated (with adjustments for the local population) that 4.0% of Nigerians in 2011 had diabetes and that the figure will rise to 4.8% in 2030 (Whiting *et al.*, 2011). Hypertension is the most common non-communicable disease in the world. About 7.1 million deaths per annum are attributable to hypertension whereas more than 1 billion individuals globally are thought to have suboptimal blood pressure (Kearney *et al.*, 2005). The prevalence of hypertension in Nigeria has risen from 10% in 1987 to 17-20% in 1999 and 32.8% in 2010 (Udenigwe *et al.*, 2011).

Prostatic diseases

Three main disorders afflict the human prostate, namely prostate cancer (PCa), benign prostatic hyperplasia (BPH) and prostatitis. Whereas PCa and BPH are thought to be androgen-driven, unregulated, enlargements of the prostate gland, prostatitis is known to arise due to microorganism-induced or psychosomatic stress-induced inflammation of the gland. Though the aetiologies and clinical manifestations of the three disorders vary, the etiopathologic mechanisms for PCa and BPH overlap considerably, differing essentially in the requirement for a carcinogen in prostate cancer. Both PCa and BPH are described as chronic and both are initiated early, but progress slowly. Due to the above similarities, this paper will concentrate on PCa and BPH.

Prostate cancer is the most common cancer (other than skin cancers) in men. It is currently the second leading cause of cancer-related deaths (after lung cancer) in men in the United States. In Nigeria, 6.15 – 16.5% of male cancers are of the prostate (Akinremi *et al.,* 2011). The critical rate-limiting step in prostate cancer progression is thought to be the progression of pre-malignant histological cancer (which autopsy data suggest is found in most men who are up to 70 years of age) to tumours that are clinically manifest (De Marzo *et al.*, 2007). The critical balance between androgens and oestrogens (which is obviously affected by a plethora of biochemical processes) is central to this progression.
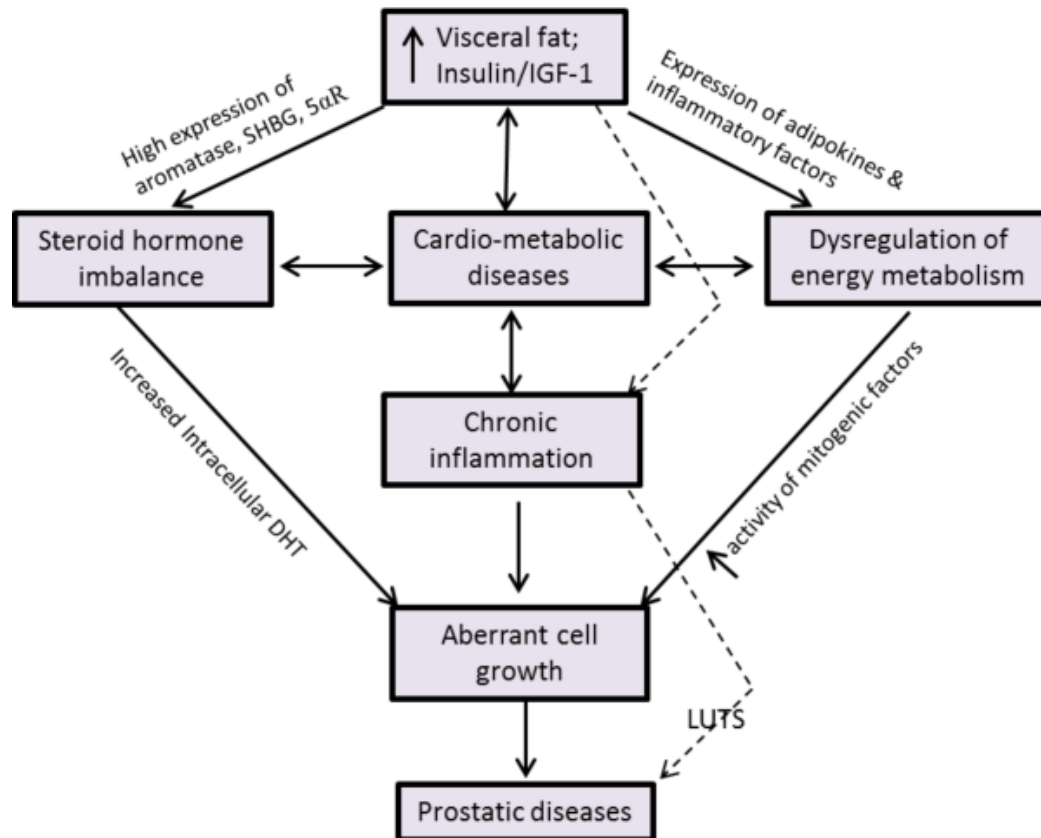
Figure 2: Link between cardio-metabolic and prostatic diseases. LUTS and DHT stand for lower urinary tract symptoms and dihydrotestosterone respectively.

BPH on the other hand is age-related but non-malignant. It is a highly prevalent disease of older men which starts as a micronodular increase in cell mass and eventually develops into macroscopic enlargement of the prostatic nodules. These cellular changes ultimately lead to bladder outlet obstruction (BOO) which in turn causes lower urinary tract symptoms (LUTS) (Briganti *et al.*, 2009; Timms and Hofkamp, 2011). BPH is thought to affect approximately 25% of men in their 50s, 33% of men in their 60s and 50% of those in their 80s (De Nunzio *et al.*, 2011a). According to Ezeanyika *et al.* (2006), 25.4% of the Nigerian male population present with symptoms suggestive of BPH In severe cases, BPH may lead to sepsis, irreversible bladder damage, renal failure or even death. In humans, BPH may exist without resulting in debilitating clinical conditions. As in prostate cancer, the degree of enlargement of the prostate in BPH (which in turn is responsible for its clinical presentation) is dependent on the delicate balance between androgens and oestrogens and their up-stream confounding factors. Figure 1 illustrates the interrelated nature of the major etiologic factors that are linked with PCa and BPH.

Links between cardiac and prostatic diseases

The possible mechanisms linking cardio-metabolic risk factors and prostate pathologies are summarised in Fig. 2. Insulin resistance arises due to a decreased responsiveness to the effect of insulin by peripheral tissues (skeletal muscle, fat, and liver). To compensate for this, more insulin is secreted, resulting in hyperinsulinemia. Hyperinsulinemia, in turn, is responsible for the production of insulin like growth factor 1 (IGF-1) in hepatocytes (Duvnkal and Duvnjak, 2009) and for the decrease in the concentration of IGF-1 binding protein (IGFBP). IGF-1, is a potent promoter of the growth of primary cultures of prostate cells and of human PCa cell lines *in vitro* (De Nunzio *et al.,* 2011b). Increased level of circulating IGF-1 is reported (from meta-analysis data) to be associated with PCa risk (Rowlands *et al.,* 2009). Furthermore, whereas transgenic mice over-expressing human IGF-1 in basal epithelial cells of the prostate have been shown to develop prostate carcinoma at a rate as high as 50% (DiGiovanni *et al.,* 2000), mice with total or liver-specific inactivation of IGF-1 show reduced prostate size and a diminished androgen-dependent prostate growth (Svensson *et al.,* 2008). Hammarsten and Peeker (2011)
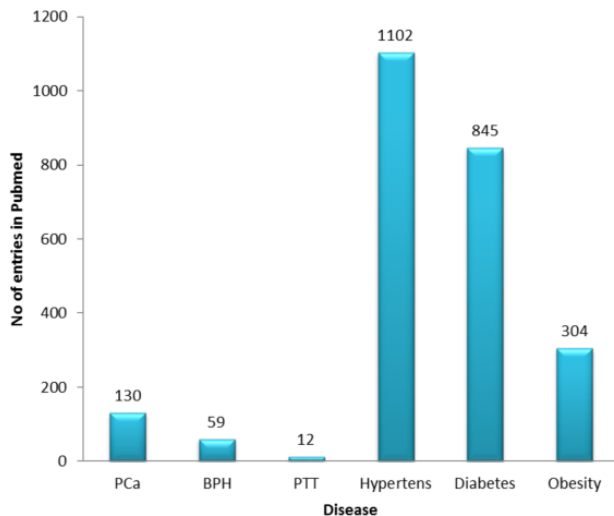
Figure 3: Disparities in research output between some cardio-metabolic and prostatic diseases in Nigeria. PCa, BPH, PTT and Hypertens stand for prostate cancer, benign prostatic hyperplasia, prostatitis and hypertension respectively. Data were collected on 2nd November, 2013.

contend that an increased insulin concentration is a common underlying abnormality that promotes both BPH and clinical PCa. Additionally, hyperinsulinemia is known to be associated with a heightened sympathetic nervous system activity which could increase smooth muscle tone within the prostate. This can result in constriction of the prostatic urethra and the attendant lower urinary tract symptoms (LUTS), independent of prostatic enlargement (Sarma *et al.*, 2009). One immediate fall-out of hyperinsulinemia is obesity, as high concentrations of insulin inhibit the action of hormone sensitive lipase, thereby preventing the mobilization of stored fat.

Visceral obesity results in the secretion of adipokines and pro-inflammatory cytokines (without prejudice to increased insulin and IGF-1 concentration in the obese state) which may mediate PCa and BPH risks. Chronic inflammation accompanies obesity and is also thought to link it to prostatic diseases. The chronic pro-inflammatory state that is typical of cardio-metabolic diseases may also contribute to PCa development and progression. Pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin (IL) 6 and IL8 are reported to be linked with increased PCa risk (Hsing *et al.*, 2007). A chronic inflammation-driven tissue remodelling, and hyperplastic overgrowth is thought to be central to BPH pathogenesis (De Nuzio *et al.*, 2011). Inflammation in the prostate leads to increased T-cell activity which causes infiltrates to accumulate within the prostate. This process can be sustained by an autoimmune mechanism, and may induce the proliferation of stromal and epithelial cells of the prostate. The repetitive process of wound healing induced by inflammation as a result of tissue

damage may also lead to the development of BPH nodules (Alcaraz *et al.*, 2009; De Nunzio *et al.*, 2011b).

Cardio-metabolic diseases are associated with a moderate, 2–3 nmol/l decrease in total testosterone in population-based studies (Grossmann, 2011). The lower testosterone levels in such subjects are often as a result of visceral adiposity and insulin resistance, via a complex bi-directional relationship (Araujo and Wittert, 2011). Visceral adiposity promotes a lowering of testosterone because adipose tissues secrete sex hormone binding globulins (SHBG) which bind testosterone, thereby making it unavailable, and low testosterone predisposes to visceral obesity, thus creating a viscous cycle that promotes insulin resistance (Grossmann *et al.,* 2010). To further compound the viscous cycle, insulin resistance results in hyperinsulinemia which, as described above, induces visceral adiposity, thereby perpetuating the cycle.

SHBG and albumin bind about 44% and 54% of testosterone respectively leaving only 2% circulating unbound (free). Only free testosterone and testosterone bound by albumin is biologically available. Increase in SHBG due to increase in visceral adipose tissues, by reducing available testosterone, causes the relaxation of the negative feedback inhibition that controls testosterone production, and more testosterone is produced. The enzyme 5α reductase is therefore provided with substrates to be converted to dihydrotestosterone (DHT), the proximal androgen in prostatic tissues (Ejike and Ezeanyika, 2009). The perpetuation of this cycle is thought to result in aberrant growth of prostatic cells, leading to BPH or PCa. Men with BPH and PCa often present with relatively low androgen to oestrogen ratios, a condition also observed in men with cardio-metabolic diseases and believed to link the two (Gorbachinsky *et al.*, 2010). It is worthy of note that testosterone therapy is known to promote favourable metabolic changes in body composition and moderate decreases in insulin resistance (Grossmann, 2011). Conversely, androgen deprivation therapy (ADT) used in managing PCa leads to increases in visceral fat mass and the attendant increase in insulin resistance (Hamilton *et al.,* 2011). This observation complicates the separation of the relative roles of testosterone and metabolic factors in prostate pathologies.

There is evidence that oestradiol is involved, independently or in synergy with testosterone as potent inducers of aberrant growth and neoplastic transformation in the prostate. Results from animal studies support the above position (Ejike and Ezeanyika, 2011; Ho *et al.,* 2011). The oestradiol/testosterone ratio increases with advancing age and increased visceral adiposity. The serum concentration of aromatase is also high under the said conditions.

It is obvious from the existing literature, that cardio-metabolic and prostatic diseases are intertwined in aetiology. Considering this link it thought that the methods used for

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prevention and management of cardio-metabolic diseases (which have positive effects on patients' symptoms and disease progression) may be applicable to BPH and PCa.

Between the goose and the gander

Whereas the literature shows that prostatic diseases are not less prevalent relative to cardio-metabolic diseases, it is surprising that the awareness of prostatic diseases, their aetiology, prevention, and management options lags far behind those of cardio-metabolic diseases in the Nigerian public. More worrisome is the yawning gap in research output between the two classes of diseases as is shown in Fig. 3. By searching the Pubmed database using keywords such as "prostate cancer, Nigeria", "hypertension, Nigeria", etc., one finds that for every paper on PCa indexed in Pubmed, there are > 8 on hypertension, > 6 on obesity and > 2 on diabetes so indexed. For every paper on BPH there are >18 on hypertension, > 14 on obesity and > 5 on diabetes indexed in Pubmed. Though Pubmed is not the only indexing database, it is unarguably a reputable one, and results of searches done in Pubmed give unequivocal insights into the subject of investigation.

The research output from scientists studying these diseases is a reflection of the activity in those areas of study, and possibly of the funding available for researchers who study those diseases. Implicit in such disparities is also a possibility of such a knowledge gap existing even among healthcare professionals who have the responsibility (at least at the primary setting) to guide their patients aright. To enhance and advance research and education on the prevention and management of prostatic diseases in Nigeria, a comprehensive template has been provided (Ejike, 2011). It is very important that the collective attitude towards prostatic diseases be challenged and altered to prevent, or at least reduce, the healthcare and economic costs inherent in not investing in the prevention and management of a disease that affects (even if potentially) a good proportion of Nigeria's male population.

Conclusion

Cardio-metabolic diseases are quite prevalent in Nigeria, and the prevalence rates are expected to rise in the years to come. Similarly, prostatic diseases are also very prevalent and may increase in prevalence and incidence in the future. There is now evidence in the literature that both cardio-metabolic and prostatic diseases are linked through the hyperinsulinemia and visceral adiposity paths. Both classes of diseases are currently thought to share common etiopathologic pathways, implying that similar preventive and management options may find usefulness for subjects on both sides. It is however worrisome that the volume of research activity and output seen in cardio-metabolic diseases is not seen in prostatic diseases. This trend however needs to change for what's good for the goose is good for the gander.

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