INTRODUCTION

Diabetes mellitus (DM) & cancer:

Diabetes mellitus (DM) is a serious and growing health problem worldwide and is associated with severe acute and chronic complications that negatively affect both the quality of life and the survival of affected individuals. The association between cancer and diabetes has been investigated extensively and most of the studies found that DM is associated with an increased risk of several types of cancer[1-8]. While for prostate cancer, a reduced incidence has been reported in diabetic patients due to their decreased testosterone levels[9]. Data was illustrated in **(Table 1)**[10].

Cancer risk is increased in diabetic patients:

Table (1): Meta-analyses on the relative risk (RR) of cancer in different organs of diabetic patients:

cancer	Study	**RR** (95% CI)
Liver[1]	13 case–control studies	2.50 (1.8–3.5)
	7 cohort studies	2.51 (1.9–3.2)
Pancreas[2]	17 case–control studies	1.94 (1.53–2.46)
	19 cohort studies	1.73 (1.59–1.88)
Kidney[a] [3]	1 cohort study	1.50 (1.30–1.70)
	1 cohort study	2.22 (1.04–4.70)
Endometrium[4]	13 case–control studies	2.22 (1.80–2.74)
	3 cohort studies	1.62 (1.21–2.16)
Colon–rectum[5]	6 case–control studies	1.36 (1.23–1.50)
	9 cohort studies	1.29 (1.16–1.43)
Bladder[6]	7 case–control studies	1.37 (1.04–1.80)
	3 cohort studies	1.43 (1.18–1.74)
Non-Hodgkin's lymphoma[7]	5 cohort studies	1.41 (1.07–1.88)
	11 case–control studies	1.12 (0.95–1.31)
Breast[8]	5 case–control studies	1.18 (1.05–1.32)
	15 cohort studies	1.20 (1.11–1.30)
Prostate[9]	9 case–control studies	0.89 (0.72–1.11)
	10 cohort studies	0.81 (0.71–0.92)

[a] Data on kidney cancer were not obtained from meta-analysis.

In diabetic patients, cancer may be favored by:

i) General mechanisms that promote cancer initiation or progression in any organ because they are due to alterations (i.e. hyperglycemia or hyperinsulinemia or drugs) that affect all tissues.

ii) Site-specific mechanisms affecting cancerogenesis of a particular organ.

The incidence of liver and pancreatic cancer is increased in DM:

Several meta-analyses indicate that the strongest association between DM and increased cancer risk is with pancreatic and liver cancer. **(Table1)**

DM & liver cancer:

Because of the portal circulation, liver cells are exposed to higher insulin concentrations than other tissues, a condition that is exacerbated in insulin resistant hyperinsulinemic type 2 diabetic individuals, but that is not present in insulin-deficient type 1 diabetic patients treated with exogenous insulin.

Most of the epidemiologic studies indicate a two to three-fold increase in hepatocellular carcinomas (HCC) in diabetic patients **(Table 1)**. It has been questioned whether diabetes is a direct risk factor for liver cancer or whether diabetes related diseases of the liver are also involved. Indeed, steatosis and cirrhosis, both well-known risk factors for HCC, are more frequent in diabetic patients. Also, the nonalcoholic fatty liver disease (NAFLD) is very common in both diabetes and obesity and even more frequent in obese-diabetic patients, occurring in over 80% of type 2 diabetic patients. Additional factors that may favor HCC in DM include hepatitis B and C virus infections, both are more frequent in diabetic subjects as compared with the nondiabetic population[11,12].

DM & pancreatic cancer:

The association between DM & pancreatic cancer may be:

1- Pre-existing diabetes (a condition possibly favoring exocrine pancreatic cancer).

2- New-onset diabetes (a possible sign of pancreatic functional damage due to a still undiagnosed pancreatic cancer).

The latter situation is so frequent that hyperglycemia and diabetes, when appearing after the age of 45–50 years, in a lean subject with no family history for diabetes, is considered an indication for pancreatic cancer screening[13,14]. Similarly, elderly subjects with new onset diabetes have a 3-year risk of pancreatic cancer nearly eight times higher than a nondiabetic person of similar age and sex[15].

Laboratory and clinical evidence suggest that diabetes caused by pancreatic cancer is due to cytokines produced by the tumor[16], rather than secondary to endocrine pancreatic tissue invasion and damage[13].

This conclusion is also supported by the observation that hyperglycemia occurs at an early stage of pancreatic cancer and is independent of tumor size and stage[13,17].

The pre-diabetes state should also be considered a risk factor for pancreatic cancer. Studies that evaluated the association between post-load glucose levels and pancreatic tumors in 35658 individuals reported a higher RR with increasing glucose tolerance impairment. After adjusting for age, race, cigarette smoking, and body mass index (BMI),

the risk progressively increased from normal subjects to subjects with slightly altered glycemia (RR=1.65) and then to diabetes (RR=2.15)[18].

The biological mechanisms underlying the association between diabetes and pancreatic cancer are unclear. Hyperinsulinemia has been indicated as a possible factor because exocrine pancreatic cells, which give rise to most pancreatic cancers, are exposed to very high insulin concentrations because of the common blood supply with the adjacent insulin secreting islets but this mechanism does not justify the excess of pancreatic cancer in insulin-treated diabetic patients or in type 1 diabetes[19].

Kidney cancer:

In diabetic patients, the increased incidence and increased mortality for kidney cancer have been attributed to both general mechanisms (hyperinsulinemia and obesity) and specific factors, mainly hypertension[20,21] and the frequent kidney diseases occurring in diabetic patients[22].

Bladder cancer:

Individuals with DM also display an increase in the risk of bladder cancer. In this case, in addition to general factors like hyperinsulinemia, the increased frequency of urinary tract infections is also likely to be involved.

Breast & endometrial cancer:

The risk of cancers of the female reproductive organs is also increased in DM. Both breast and endometrial cancer risks are increased in diabetic women. Hyperinsulinemia may increase the levels of bioactive estrogens by decreasing the concentration of circulating sex hormone-binding globulin and might also stimulate androgen synthesis in the ovarian stroma (proved in Kaaks study in 1996)[23]. Other possible mechanisms include delayed menarche, especially in type 1 diabetic women, who also have a higher incidence of nulliparity, irregular menses, and fertility disorders.

Colorectal cancer:

Type 2 diabetes has been associated with an increased risk of colorectal adenomas and carcinomas in most of the studies[24,25].The risk is increased in both women and men for both colon and rectal cancer[5].

The cause may be due to hyperinsulinemia, slower bowel transit time and, elevated fecal bile acid concentrations that occur in DM.

Non-Hodgkin's lymphoma:

Large prospective cohort studies and case–control studies have shown a moderate increase of non-Hodgkin’s lymphoma in diabetic patients, a possible consequence of the immune dysfunction related to impaired neutrophil activity and abnormalities in cellular and humoral immunity in diabetes[7].

Decreased incidence of prostate cancer in diabetes:

In contrast to the increased risk of numerous forms of cancers, most studies report a reduced risk of prostate cancer in men with diabetes. A recent meta-analysis[9] including 14 studies carried out in the pre-PSA era (i.e. before the generalized use of prostate specific antigen screening for prostate cancer)[26]and 5 additional studies carried out in the PSA era (and therefore, concerning cancers diagnosed earlier and smaller cancers) has found a significantly reduced risk in diabetic patients **(Table 1)**. The 16% average decreased risk of developing prostate cancer is due to the decreased testosterone levels in diabetic patients[27]. However, other metabolic and hormonal factors, including altered insulin and leptin concentrations, the diffuse use of medications such as statins and metformin, and changes in diet and lifestyle in order to control diabetes, have also been hypothesized as elements potentially contributing to the inverse association between diabetes and prostate cancer[9].

Mechanisms by which DM increases risk of cancer:

The role of hyperinsulinemia in favoring cancer incidence and progression in diabetic patients:

Diabetes is generally characterized by hyperglycemia and hyperinsulinemia, often coupled with a reduced metabolic effect of insulin (insulin resistance) in peripheral tissues. Chronic hyperinsulinemia, however, is a possible factor favoring cancer initiation and/or progression in diabetic patients due to the mitogenic effect of insulin. One example is the potentially increased risk of lung cancer in diabetic patients using the recently introduced inhaled insulin[28].

There are multiple and complex mechanisms potentially responsible for the mitogenic effects of insulin.

First, when insulin levels increase (as in the postprandial surge in insulin-resistant subjects or after insulin injection), insulin may bind and activate the related insulin-like growth factor-I (IGF-I) receptor, which shares about 80% homology with the insulin receptor (IR), but has a more potent mitogenic and transforming activity. Moreover, insulin decreases IGF-I-binding proteins (IGF-BP1 and, perhaps, IGF-BP2)[29], this will result in increased free IGF-I, the biologically active form of the growth factor.

Secondly, many cancer cells have an increased IR content The IR may be expressed in two different isoforms, A and B, produced by an alternative splicing of the IR gene transcript. In malignant cells, the A isoform (IR-A) expression is predominant [30]and its activation elicits more mitogenic than metabolic effects. By binding to the over-expressed IR-A, insulin may favor cancer progression and facilitate the growth of tumors.

Finally, insulin mitogenic activity might be enhanced at the cellular level by post-receptor molecular mechanisms, including insulin residence and the intracellular up-regulation of the insulin mitogenic pathway[31].

Anti-diabetic drugs that may influence cancer risk in diabetic patients:

The three major oral anti-diabetic drug families (sulphonylureas, biguanides, and thiazolidinediones) have a different mechanism of action.

Sulphonylureas stimulate endogenous insulin secretion, while the other two categories of compounds are insulin sensitizers, i.e. they make tissues more responsive to insulin and, therefore, decrease hyperinsulinemia.

The biguanide metformin, widely used for more than 30 years and currently suggested as first-line therapy in type 2 diabetic patients, has been reported to reduce cancer risk (odds ratio=0.86) when compared with untreated patients [32]. In addition to lowering the amount of circulating insulin, another possible mechanism for the anti-cancer effect of metformin is the stimulation of adenosine mono-phosphate kinase (AMPK)(an enzyme inducing glucose uptake by muscles) and its upstream regulator liver kinase b1 (LKB1), a well-recognized tumor suppressor protein[33].

AMPK activators act as antiproliferative agents because they reduce insulin (and IGF-I) signaling downstream of the receptor and therefore, inhibit insulin-stimulated proliferation [34,35]. Data on the other insulin-sensitizing drug (thiazolidinediones) are more controversial. A beneficial[36], neutral[37]or even deleterious[38]effect has been reported for different types of cancer. The biological mechanism of these compounds is to activate peroxisome proliferator-activated receptor gamma (PPARγ) receptors which in several in vitro experimental models has shown a potential anticancer effect[39].

The third group of drugs (sulphonylureas) are secretagogues, i.e. increase insulin secretion and cause hyperinsulinemia and they have been associated with an increased risk of cancer[40].

Other factors that may influence the risk of cancer in diabetes:

Obesity:

Over 80% of type 2 diabetic patients are obese. Obesity is associated with a higher incidence and a higher mortality in cancer[41,42].

Among the many possible mechanisms involved, hyperinsulinemia (which is typical of central obesity), diet and nutritional factors causing a positive energy balance, also other hormone abnormalities have been indicated as causal factors.

Hyperglycemia:

It is known that a high intake of sugar and refined carbohydrates and elevated blood glucose levels are strongly associated with the risk of cancer[43].

Possible mechanisms implicated include the role of an abnormal energy balance and the effect of hyperglycemia in impairing the effect of ascorbic acid on the intracellular metabolism and reducing the effectiveness of the immune system. Further evidence suggests a role for the oxidative stress-responsive genes (like thioreodoxin-interacting protein) that are sensitive to hyperglycemia and regulate the level of reactive oxygen species (ROS)[44].

Free fatty acids:

Desregulation of fatty acid synthase (FASN) activity, which catalyzes de novo fatty acids biogenesis could also play a role in the pathogenesis of insulin resistance, diabetes, and cancer[45].

Chronic inflammation and oxidative stress:

The metabolic abnormalities that characterize diabetes, especially under conditions of poor metabolic control, increase oxidative stress and cause a permanent pro-inflammatory condition. High concentrations of diverse free radicals and oxidants generate a potent reactive oxygen species (ROS) that can damage cell DNA by direct oxidation or by interfering with the mechanisms of DNA repair[46].

ROS may also react with proteins and lipids, forming derivative products that may alter intracellular homeostasis favoring the accumulation of mutations that can contribute to the multistage carcinogenesis process[47].

A possible additional mechanism is related to mitochondrial dysfunction, a well-recognized abnormality in diabetes. DNA repair is a high energy consuming process that requires increased mitochondrial activity: stimulating malfunctioning mitochondria will not only provide low insufficient energy supply but also increase ROS production[48].

Moreover, an additional factor correlated with insulin resistance is the pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) produced by the adipose tissue[49], TNFα induces development and progression of many tumors[50], by strongly activating nuclear factor-kappa B (NF-κB), which mediates many of the pro-tumoral effects of TNFα.

DM & PSA:

Diabetics appear to have a lower PSA than non-diabetics & this is consistent with previous cross-sectional findings suggesting that serum PSA levels are lower among diabetic men than among non-diabetic men. Specifically, Muller et al[51], who found men with elevated and highly elevated hemoglobin A1c levels had 15% and 29% lower serum PSA levels, respectively. Men who were on insulin treatment and oral diabetic medications also had lower serum PSA concentrations[51].

Using The National Health and Nutrition Examination Surveys, Werny and colleagues found 22% lower average serum PSA levels among men with type 2 diabetes[52].

These findings were further replicated by Fukui et al[53], Who observed 10%-16% lower average serum PSA levels among male Japanese diabetics, ages 50-79 years.

The association between diabetes and serum PSA levels seems to vary with the duration of diabetes. Several studies have found an inverse relation between diabetes duration and serum PSA levels[52,54]. It was found that as the duration of diabetes increases, the action of insulin decreases, resulting in subsequent drops in serum PSA levels. This is supported by findings that later-stage diabetes is characterized by insulin resistance and lower levels of circulating insulin, which have been associated with lower prostate-cancer risk and serum PSA levels[54,55].

A lower risk in later-stage diabetes may be attributable to the androgen regulation of PSA levels. PSA cleaves insulin growth factor binding protein 3, a major binding protein for insulin growth factor 1, which is involved in insulin signaling and associated with an increase in prostate cancer risk[56].

Diabetic men have lower androgen levels than nondiabetic men, and this may partially explain their lower PSA levels[27].

Diabetes might also alter PSA values through impaired kidney function[57], or as a consequence of diabetes medication use such as metformin which has been shown to decrease testosterone levels in nondiabetic men but not in diabetic men [58,59].

PSA in Arabs:

For Arab men, the normal median total PSA level of 0.45 ng/ml is lower than the 0.8 ng/ml reported in 1995 for Japanese men[60].In 1993, Oesterling et al[61], and Dalkin et al[62], developed age specific reference ranges for serum PSA levels for White men from the USA; the reference ranges are higher than for Japanese men, which in turn are higher than for Arab men **(Table 2)**.

Table (2): Comparison of serum PSA levels as a function of age in healthy White men from the USA[61], Japanese[60], Chinese[63] and Arab men[64]:

Age range (years)	PSA in USA white(ng/ml)	PSA in Japanese(ng/ml)	PSA in Arab(ng/ml)	PSA in Chinese(ng/ml)
40–49	0-2.5	0-2	0-0.9	0-1.2
50-59	0-3.5	0-3	0-1.6	0-2.4
60-69	0-4.5	0-4	0-2.9	0-3.2
70-79	0-6.5	0-5	0-5.5	0-3.4

Chinese men appear to have the lowest age-specific reference ranges for PSA levels, as reported by He et al[63]**(Table 2)**. For each age group, from 40–79 years, the upper limit of normal for serum PSA levels for Arab men is lower than in Japanese or in White men. The clinical implication of this finding is that the serum PSA value for an Arab man has a different clinical meaning than the same value for similarly aged Japanese or a White man. Hence, whereas a PSA level of 2 ng/ml will be considered normal for a White man or a Japanese man aged 40–49 years, for an Arab man of the same age and PSA value, the possibility of prostate cancer needs to be excluded.

The Japanese PSA values were measured with the IMx PSA assay (Abbott Laboratories, Abbott Park, IL, USA) and those of the White men reported by Oesterling et al in 1993[61], by the Tandem-R PSA assay (Hybritech Inc. San Diego, CA, USA), whereas in Arabs a third generation Immulite kits were used. However, it is unlikely that the lower values in Arab men can be attributed solely to the diagnostic kits used as Jacobsen et al[65] Showed in 1995 that, PSA is fairly stable, especially if the serum has been separated early after blood sample collection and stored appropriately. This implies that the assay technique should not substantially affect the values of PSA measured, and this was confirmed by Junker et al. in 1997[66], who compared four different total and free PSA

assays and found no significant difference in the mean values obtained, especially when the total PSA level was < 25 ng/ml. Furthermore, as prostate glands in Arab men are smaller than in White or Japanese men, and as it is known that the larger the prostate the higher the PSA level, the smaller prostates in Arab men is the most likely explanation for the low PSA levels.

DM & prostate volume:

Diabetics seem to have larger prostatic volumes if compared with non-diabetics, although DM type 2 & BPH are apparently disparate clinical entities, both diseases seem to be sharing similar epidemiologic features, which are possibly connected to a common pathogenic pathway related to aging and diet[67]. In 1966 Bourke and Griffin were the first to suggest an association between diabetes mellitus and BPH etiology, based on the higher prevalence of diabetes mellitus among men subjected to prostatectomy than in the general male population [68]. Almost 30 years later, a study by Hammarsten et al regenerated the scientific interest on the association between these two conditions[69]. They showed that patients with lower urinary tract symptoms (LUTSs) and DM type 2 had larger prostate volumes than patients with LUTSs without diabetes mellitus[69]. In addition, Safarinejad and Sarma found a positive association between clinical markers of BPH and diabetes mellitus[70,71]. Interestingly, other researchers recognized that from patients with hypertrophy of prostate those with the higher levels of serum glucose (>110 mg/dl) had a considerably higher mean prostate volume in comparison with patients with low levels of serum glucose[72,73]. Also it seems that insulin can affect BPH & this was evident in Barnard et al study who connected the reduction of growth of stem epithelial prostate cells with the reduction of insulin[74]. Among other possible mechanisms proposed to associate the development of BPH with DM type 2 are the increase of the peripheral sympathetic nerve tone and the activity of autonomous nervous system in general due to hyperinsulinemia[75], and hypoxia as a result of the decreased blood supply of the prostate deriving from diabetes mellitus induced vascular damage[76]. Current knowledge supports the idea of a growth-stimulating factor mediating the development and maintenance of the hypertrophic prostate. In fact, insulin is a growth-stimulating hormone that stimulates growth and cell reproduction. In order to evaluate the role of activating factors of BPH growth, Wang et al investigated the expression of fibroblasts growth factor (fibroblast growth factor2, FGF2) in the prostates of a capable number of rats with experimental-induced diabetes mellitus. They found that the expression of FGF2 was higher in epithelial cells compared to that of the stromal cells of the prostates of the control group; however, the expression of FGF2 was uniformly distributed in the prostates of diabetic group. Interestingly, the presence of FGF2 in the stromal and the epithelial layers was consistent with the disproportion in the relation of number of cells of epithelial and stromal layers that is observed in BPH. They also noticed that while the diabetic rats had smaller prostates and lower levels of serum testosterone compared to those of the control group, treatment with insulin increased both the size of prostate and the levels of testosterone[76].

Prostatic volume in Arabs:

Arabs seem to have small prostates **(Table 3)**

Table (3): Comparison of prostate volumes as a function of age in healthy White men from the USA[61], Japanese[60], and Arab men[64]:

Age range (years)	Prostate volume range in USA white(ml)	Prostate volume range in Japanese(ml)	Prostate volume range in Arab(ml)
40-49	13-51	9-33	8-22
50-59	15-60	9-35	9-27
60-69	17-70	10-37	9-30
70-79	20-82	11-40	10-33

P< 0.001 (Arab vs USA White), P < 0.06 (Arab vs Japanese).
P calculated using Student's t -test.

Also in 1998 from local experience of TURP for BPH in Arab men over a 10-year period, the prostate causing symptoms of bladder outlet obstruction (BOO) is smaller than in Caucasians, and histology tends to show that the prostate has more stromal elements and fewer glandular elements than found in Caucasians[77].

DM & testosterone:

There is an inverse relationship between testosterone levels and diabetes, where men with diabetes have lower testosterone levels compared to men without a history of diabetes[78-80].

Subnormal free testosterone concentrations in association with inappropriately low LH and FSH concentrations and a normal response to GnRH of LH and FSH in type 2 diabetes were first described in 2004[81].

These abnormalities were independent of the duration and severity of hyperglycemia [glycosylated hemoglobin (HbA1c)]. Magnetic resonance imaging in these hypogonadal patients showed no abnormality in brain or the pituitary [81]. This association of hypogonadotropic hypogonadism (HH) with type 2 diabetes has now been confirmed in several studies and is present in 25–40% of these men[79,80,82,83]. In this context, it is important that The Endocrine Society now recommends the measurement of testosterone in patients with type 2 diabetes on a routine basis[84].

Type 2 diabetic men with low testosterone levels have also been found to have a high prevalence of symptoms suggestive of hypogonadism such as fatigability and erectile dysfunction [80]. HH is relatively rare in type 1 diabetes and, therefore, is not a function of diabetes or hyperglycemia *per se*[85].

Possible Pathophysiological Mechanisms Underlying HH in Type 2 Diabetes

Role of estradiol:

Because testosterone and androstenedione in the male can be converted to estradiol and estrone, respectively, through the action of aromatase in the mesenchymal cells and preadipocytes of adipose tissue, it has been suggested that excessive estrogen secretion due to aromatase activity in the obese may potentially suppress the hypothalamic secretion of GnRH[86]. This hypothesis was examined in a study that compared the estradiol concentrations in 240 type 2 diabetic men with and without HH[87].

Role of insulin resistance:

The selective deletion of the insulin receptor from neurons in mice leads to a reduction in LH concentrations by 60–90% and low testosterone concentrations[88]. These animals respond to GnRH challenge by normal or supernormal release of LH. In addition, these animals had atrophic seminiferous tubules with markedly impaired or absent spermatogenesis. In addition, it is known that the incubation of hypothalamic neurons with insulin results in the facilitation of secretion of GnRH[89,90]. Thus, insulin action and insulin responsiveness in the brain are necessary for the maintenance of the functional integrity of the hypothalamo-hypophyseal-gonadal axis.

Role of inflammatory mediators:

TNF-α and IL-1β have been shown to suppress hypothalamic GnRH and LH secretion in experimental animals and *in vitro*[91,92]. It is therefore relevant that C-reactive protein (CRP) concentrations are markedly increased in hypogonadal type 2 diabetic men compared with men with type 2 diabetes and normal testosterone (6.5 *vs.* 3.2 mg/liter)[93].

These data were confirmed by another study from Australia in which the median CRP concentration in type 2 diabetic patients with low total testosterone was 7.7 mg/liter compared with 4.5 mg/liter in men with normal testosterone[83]. Free testosterone concentrations were inversely related to CRP concentrations ($r = -0.27$; $P = 0.02$). It is thus possible that inflammatory mediators may contribute to the suppression of the hypothalamo-hypophyseal axis and the syndrome of HH in type 2 diabetes.

The presence of inflammation may also contribute to insulin resistance because several inflammation-related mediators, such as suppressor of cytokine signaling-3, IκB kinase β, and c-Jun N-terminal kinase-1 interfere with insulin signal transduction[94,95] and contribute to insulin resistance.

Testosterone in Arabs:

Low testosterone levels are observed in Arabs as showed in Kehinde et al. study[96], where Serum levels of total testosterone, (TT), sex hormone binding globulin (SHBG), free androgen index (FAI); adrenal C19-steroids, dehydroepiandrosterone sulphate (DHEAS) and androstenedione (ADT) were obtained from 329 unselected apparently healthy Arab men (Kuwaitis and Omanis) aged 15–80 years , hormones were determined using Immulite kits (Diagnostic Systems Laboratories Inc, Webster Texas, USA), The results that were obtained in Arab men were compared with those reported for similarly aged Chinese, German and White USA men. In all four ethnic groups, median total testosterone (TT) and

free androgen index (FAI) declined with age, while sex hormone binding globulin (SHBG) increased with age. However, the mean TT and SHBG was significantly lower ($p<0.01$) and the FAI significantly higher in Arab men ($p<0.01$) compared to German men only in 21–30 years age group. In the other age groups the levels of TT and SHBG were higher in the Germans but the differences were not statistically significant. The mean TT and SHBG were significantly lower in Arab men compared to Caucasian men especially in early adulthood. Caucasians have significantly higher serum levels of the precursor androgens dehydroepiandrosterone sulphate DHEAS and ADT especially in early adulthood compared to Arab men. These observations of low circulating androgens and their adrenal precursors in Arab men may partially account for the decreased risk for prostate cancer among Arab men.

BMI & PSA:

Although much of the effect of obesity on prostate cancer is unclear, multiple studies have shown an inverse relationship between serum PSA levels and BMI. A population-based study examined the association between BMI and PSA levels in nearly 3000 men without prostate cancer[97]. The authors found that the mean PSA level decreased with increasing BMI, such that the mean PSA level in men with a normal BMI (18.5 - 24.9 Kg/m^2) was 1.01 ng/ml and in morbidly obese men (BMI $\geq$ 40 Kg/m^2) was 0.69 ng/ml. The author reported that age and race did not affect the association between PSA levels and BMI. The authors hypothesized that lower levels of circulating androgens in obese men might be responsible for the observed lower levels of PSA[97].

Fowke et al [98] examined approximately 300 men in a community-based cancer screening cohort, and found an inverse relationship between BMI and PSA levels in both Caucasian and African-American groups.

By contrast, Loeb et al [99] found that total PSA increased with an increasing BMI in a cohort of nearly 600 men who underwent radical prostatectomy (RP) by a single surgeon. The authors also discovered that men with a higher BMI were also more likely to have a PSA velocity > 2 ng/ml/year, a value associated with a higher risk of death from prostate cancer[100]. Similarly, in a multi-institutional cohort of men undergoing RP, there was no association between BMI and preoperative PSA levels[101]. Other studies that have shown an inverse association between BMI and PSA levels have included cohorts of men without prostate cancer. It is possible that the presence of prostate cancer attenuates any biological or hormonal influences of high BMI on serum PSA levels.

Other studies have not confirmed an independent effect of BMI on serum PSA levels[102]. No clear correlation between BMI and either the total concentration of PSA or the percentage of free PSA was found in a cohort of more than 500 men involved in a community-based screening program for prostate cancer[103]. The majority of the participants were overweight (46% of participants had a BMI of 25-29.9 kg/m^2) or obese (13% of participants had a BMI > 30 kg/m^2). Fowke et al[98] found that, while BMI was inversely associated with total PSA levels in their cohort, percentage of free PSA was not associated with BMI[98]. In addition, Kristal et al[104] did not find an association between BMI and PSA velocity in men without prostate cancer in the placebo arm of the prostate cancer prevention trial[104].

In a study of more than 6000 healthy Korean volunteers, analysis showed that increasing BMI was associated with a decreased risk of having a PSA level > 2.5 ng/ml; however, the association did not hold up in statistical analysis[105]. The lack of association between BMI and PSA levels in this study might be due to the lower median BMI (24 kg/m) and younger median age (47 years) of this population compared with other studies. The association between BMI and PSA levels in other studies might not have been apparent in this younger and thinner cohort[105].

BMI & prostate volume:

Studies have shown that there are variations in prostate size with increasing degrees of obesity. Serum levels of insulin and leptin, BMI and abdominal obesity were compared in 200 men with benign prostatic hyperplasia (BPH) scheduled to undergo surgery and 302 controls[106].

Abdominal obesity, measured by waist-to-hip ratios and elevated serum insulin levels were associated with an increased risk of BPH. In a population of men with lower urinary tract symptoms, obesity and high fasting insulin levels were associated with increased prostate sizes and prostate growth rates[107]. In the previously mentioned multi-institutional study of men undergoing RP, increasing BMI was associated with larger prostate size, but only in men younger than 63 years with a BMI < 35 kg/m^2.[101] Loeb et al did not find an association between BMI and prostate size at RP[99]. Obesity and the metabolic syndrome might alter levels of multiple hormones and growth factors (e.g. testosterone, estrogen, letpin, insulin and insluin-like growth factor-1) with competing effects on prostate growth and size, such that the overall effect is variable or unknown, especially for individual patients.

In summary, it is apparent that obese men with a low risk of developing prostate cancer have lower serum PSA levels than their non-obese counterparts; the presence of prostate cancer might attenuate this trend. The effect of obesity or the metabolic syndrome on PSA derivatives, such the percentage of free PSA and PSA velocity, is unclear. Obesity might result in increased prostate size owing to BPH, but its effect on the cancerous glands removed during RP does not seem to be uniform.

BMI & serum testosterone:

It has been hypothesized that men with obesity have a different sex steroid hormonal status, in particular, lower serum testosterone levels compared with those with a normal body composition[108].

The serum testosterone concentrations are decreased in obese men in proportion to the degree of obesity, implying an inverse correlation between the BMI and serum testosterone level[109]. Alterations in other sex steroids such as sex hormone-binding globulin (SHBG), inhibin B, and estradiol have also been described[110].

MacDonald et al [110] performed a systematic review with meta-analysis on the impact of BMI on reproductive hormones and semen parameters in human males. The authors found strong evidence for a negative relationship between BMI and both testosterone and SHBG. The strength and consistency of relationships for these hormones across different populations, age ranges and BMI samples supported this conclusion[110].

For SHBG, this relationship is probably explained by reduced hepatic globulin synthesis due to inhibition by excessive circulating insulin in men with higher BMI[110]. This explanation was shown by Pasquali et al [111] who studied the effects of obesity on infertility and demonstrated that fertility can be negatively affected by obesity and the main factors implicated in this association may be insulin excess and insulin resistance[111].

Also, as mentioned above, there is also evidence that there is a negative relationship between free testosterone and BMI. However, this relationship appears to be weak. One small study has gone as far as to suggest that free testosterone remains within normal ranges in overweight and even moderately obese men, although in severely obese men the levels are sub-normal[112].

The studies that undertook more comprehensive clinical examination when studying the relationship between obesity and testosterone levels did not observe clinical signs of hypogonadism, even in those with significantly reduced free testosterone[108,113]. It is therefore suggested that a reduction in free testosterone in overweight and obese men has little biological effect, consistent with MacDonald et al[110] finding that there is no detectable relationship between BMI and semen parameters.

Pathophysiologic mechanisms leading to alteration of testosterone levels in obese men:

Obesity is not only associated with lower total testosterone levels, but also is associated with lower free testosterone levels[114,115]. The level of decrease in androgen levels is proportional to the degree of obesity[112,116].

The mechanisms accounting for reduced total testosterone levels are various and are defined within a reversible hypogonadotropic hypogonadism pathway[117].

Increased estrogens levels

The reduced pituitary function or hypogonadotropic hypogonadism in obese men is likely multifactorial. It is known that in obese men both estrone and estradiol are increased due to increased peripheral aromatization of androgens[118]. Estrogens have a negative effect on the hypothalamus that alters the gonadotropin-releasing hormone (GnRH) pulses and suppresses gonadotropin (follicle-stimulating hormone "FSH" and luteinizing hormone "LH") secretion[119]. Such a role for estradiol is also confirmed showing an increase in gonadotropins and sex steroid production after the administration of aromatase inhibitors to obese men[120].

The relation between increasing BMI and elevated serum levels of estradiol was challenged in a group of men with type 2 diabetes. In this study, serum estradiol levels were not correlated to BMI but were correlated to the substrate of the aromatase enzyme, serum testosterone[87].

Polymorphism of the aromatase enzyme

It was demonstrated that genetic polymorphisms, such as the TTTA polymorphism of the aromatase enzyme, could modulate the relation between obesity and serum estradiol levels in men. Higher TTTAn repeats were associated with an enhancement of the interaction between weight and estradiol levels. The correlation between weight and

estradiol level was statistically significantly seen among men homozygous for higher TTTAn repeat numbers, whereas no such correlation is evident for men homozygous for lower numbers of repeats. Interestingly, after 2 years of follow-up, weight loss was associated with reduced serum estradiol levels only in men with higher TTTAn repeat numbers[121]. This effect of the aromatase polymorphism was also found to influence the relation between weight and abnormal semen parameters. Men with high TTTAn numbers were more likely to show semen alteration in relation to increasing weight[122].

Endogenous opiods

Other factors, different from hyperestrogenemia, have been proposed to explain the hypogonadotropic hypogonadism seen in obesity[112,123]. Blank et al showed that GnRH infusion caused a significant increase in LH levels in both obese and normal weight men. After infusion of naloxone, LH levels increased only in obese men and not in normal weight men. In obese men, LH pulse frequency after naloxone increased by 51% from baseline. These results suggest a role for endogenous opioids in the pathophysiology of hypogonadotropic hypoandrogenism in extremely obese males[124]. The effect of type 2 diabetes, frequently associated with obesity, on the hypothalamic-pituitary-gonadal axis is increasingly being appreciated[125].

Sleep apnea

Sleep apnea, more common among the obese, was also proposed to affect morning serum testosterone levels negatively in men[126,127]. It was found that the adjusted means (corrected for age and BMI) of total testosterone is reduced proportionally to the severity of the sleep apnea. After correction for age and BMI, other parameters of sleep apnea were also negatively correlated with total and free testosterone levels[128]. Sleep apnea can affect both testosterone levels (with potentially altered spermatogenesis) as well as, independently, erectile function. The combination of both factors may result in a compounding effect on male fertility[126-130].

Insulin resistance

Obese men and men with type 2 diabetes can have secondary hypogonadism because of the peripheral and central insulin resistance and the effect of proinflammatory cytokines (TNFα and IL-6) on the hypothalamic-pituitary-gonadal axis[131]. Sex hormone-binding globulin (SHBG) levels are reduced in obese men as a result of increased circulating insulin levels associated with the insulin resistance of obesity[132]. However, after adjusting for SHBG levels, low testosterone levels have been shown to be correlated with insulin resistance and obesity, denoting an independent effect of insulin resistance on testosterone production[133].

Direct effect on testicular function

Male obesity is associated with increased circulating estrogens. Estrogens may have a direct deleterious effect on spermatogenesis[134]. Additionally, a negative effect of environmental toxins and endocrine disruptors possessing estrogenic activities on male fertility have been suggested[135].

Serum levels of multiple organochlorines were positively correlated to male BMI and to infertility[136]. These toxins are fat soluble and tend to accumulate in the fatty tissue[137].

Sedentary life, prolonged sitting, and fat deposition in the lower abdomen can reduce male fertility, likely through increased testicular temperature to the level of body core temperature[137]. Obesity was also shown to be associated with high homocysteine and low vitamin D levels. Both are suspected to affect semen parameters[138].