DISCUSSION

The mean PSA value in the present study was 3.02 ± 1.89 ng/ml which is comparable to Hanash et al[152] mean PSA value which was 4.14 ng/ml among patients at the same age group of the present study. Also, they showed that among Saudi men, the mean serum PSA levels (4.14 ng/ml) are considerably higher than those reported in Western countries (2.76 ng/ml), although with no evidence of prostate cancer.

Among other studies that targeted Arabs, Kehinde et al[153] evaluated the mean PSA values among Kuwaitis and reported a mean value of 4.79 ng/ml among patients at the same age-group of the present study, which is a value that is also comparable to the present study.

Most studies performed in the Middle East, including the present study, showed higher mean PSA values than in the USA and Europe. In the Western societies the risk of prostate cancer is considered high in men with such PSA levels. However, in the Middle East, the incidence of prostate cancer is relatively low[152,154,155].

This phenomenon was hypothesized to be a result of higher incidences of BPH, or BPH with prostatitis which may alter the prostatic epithelial lining which is the main source of PSA and one study showed that compared with Caucasians in the USA and Europe, BPH and BPH with prostatitis appear to be more frequent causes of elevated serum PSA levels in Arab men than prostatic cancer[156].

In this study diabetics had lower PSA values than non-diabetics and this may be due to their lower androgen levels[27]. Our finding of a significant downward trend of PSA in diabetics is consistent with a possible association between progressing diabetes and decreasing testosterone concentrations (which was evident in our study), which may lower the risk of prostate cancer[157]. Serum PSA may be associated with testosterone in men with subnormal levels of the sex hormone[158], as is the case with diabetic men. Diabetes might also alter PSA values through impaired kidney function[57] or as a consequence of diabetes medication use. Metformin, a hypoglycemic agent, has been shown to decrease testosterone levels in non-diabetic men but not in diabetic men[58, 59].

Our finding that the change in serum PSA levels was associated with diabetes 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.

Our results suggest that men with diabetes have slower increases in serum PSA levels over time, and this might account for the lower serum PSA levels observed among diabetics in cross-sectional studies. As noted in the introduction, the association between diabetes and serum PSA levels is hypothesized to vary with the duration of diabetes.

Several studies have found an inverse relation between diabetes duration and serum PSA levels[52,54].

It is plausible 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[56,159]. Previous findings that show use of diabetic medication is associated with serum PSA levels also support this hypothesis, as diabetic medication use may be a proxy for diabetes severity[51].

It remains to be demonstrated whether or not decreases in serum PSA levels drive the lower risk of prostate cancer observed among diabetic men in previous studies[9,160-162]. If smaller increases in serum PSA levels among diabetics result in less detection of prostate cancer among asymptomatic cases, it might suggest a detection bias among diabetic men, similar to that thought to exist among obese men due to their lower serum PSA levels and increased prostate volumes[163,164].

Furthermore, if the smaller increase in serum PSA levels among diabetic men delays the diagnosis of prostate cancer, men with diabetes may be more likely to be diagnosed with later-stage disease. As such, the potential impact of diabetes on prostate-cancer detection warrants further investigation in future studies.

In our study diabetics were found to have lower testosterone values than non-diabetics and this was consistent with the studies over the last few years that clearly established that there is an inverse relationship between testosterone levels and diabetes. Men with diabetes have lower testosterone levels compared to men without a history of diabetes[78-80].

The Endocrine Society, therefore, now recommend the measurement of testosterone in patients with type 2 DM on a routine basis[84].

A systematic review and meta-analysis of cross-sectional studies indicated that testosterone levels are significantly lower in men with type 2 diabetes (mean difference, -76.6 ng/dl; 95% confidence interval [CI], -99.4 to -53.6). Similarly, prospective studies showed that men with higher testosterone levels (range, 449.6–605.2 ng/dl) had a 42% lower risk of type 2 diabetes (RR, 0.58; 95% CI, 0.39 to 0.87)[165].

Somewhat surprisingly, the nature of the hypogonadism associated with diabetes mellitus type 2 appears to be hypogonadotropic[81]. Also obesity, very high C-reactive proteins concentrations, and mild anaemia are contributing factors in hypogonadism that is present in diabetics.

In this study diabetics had larger prostates than non-diabetics. 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. They showed that patients with lower urinary tract symptoms (LUTSs) and type 2 DM 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 among 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]. Furthermore, Hammarsten and H¨ogstedt comparing anthropologic characteristics with laboratory and clinical data in patients with lower urinary tract symptoms with or without manifestations of the metabolic syndrome demonstrated a further increase in prostate growth rate with the increased levels of serum insulin[166]. This observation was confirmed by Ozden et al. who found considerably higher annual rates of increase in the volume of the transient area of diabetics against the patients with low levels of serum glucose[72], and this was consistent with our study where there was a positive association between duration of diabetes and prostate size. Nandeesha et al. correlated insulin profile parameters with prostate size and found fasting serum insulin and insulin resistance levels significantly higher in non-diabetic-BPH cases when compared to controls[167]. Also, Barnard et al. 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 type 2 DM are the increase of the peripheral sympathetic nerve tone and the activity of autonomous nervous system in general due to hyperinsulinemia[75] and hypoxia, due to the decreased blood supply of the prostate deriving from diabetes mellitus induced vascular damage[76]. Taking in consideration the above information, it could be assumed that abnormalities of glucose homeostasis could play a role in the cause of BPH by influencing the proliferation rate of prostate cells. Also, growth-stimulating factors may be from the possible causes of BPH development in diabetics. In fact, insulin is a growth-stimulating hormone that stimulates growth and cell reproduction. The presence of growth factors for prostatic tissue and their role in cellular interactions is known from older studies[75]. 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 peer 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].

The study at hand has shown an inverse relationship between the mean values of PSA and the BMI of the recruited subjects, this finding was statistically correlated and revealed a negative strong correlation.

Accordingly, this finding was confirmed in multiple large-scale studies in various regions of the world.

In 2010, a group of Korean investigators searched the effect of body mass index (BMI) and waist circumference (WC) on prostate specific antigen (PSA) and prostate volume[168]. The study included 10,380 men aged from 30 to 79 years old who received routine comprehensive health evaluations from March 2004 to June 2009 at a health care center at Seoul National University Hospital in South Korea. This study targeted generally healthy men. BMI and waist circumference were found to be negatively associated with PSA in all age groups, and the results was not affected by prostate volume. BMI and WC were also positively associated with prostate volume in all age groups (similar also to the present study results).

In conjunction, Price et al[169] studied the relationship between BMI, PSA and digital rectal examination findings among participants in a prostate cancer screening clinic. A total of 544 consecutive participants volunteered for screening consisting of a PSA test and a DRE performed by the urologist. They abstracted clinical information retrospectively from a self-administered questionnaire assessing age, race, education, vasectomy history, family history of prostate cancer, recalled weight at age 18, and current height and weight. The researchers found that increased BMI was associated with lower PSA values in the studied subjects. The mean PSA reported for normal weight men was 2.2 ± 2.0 ng/ml, for overweight men was 2.2 ± 1.8 ng/ml and for severely obese men was 1.6 ± 0.2 ng/ml.

Similarly, Baillargeon et al[97] studied the association of body mass index and prostate-specific antigen in a population-based study in nearly 3000 men without prostate cancer. The authors found that the mean PSA level decreased with increasing BMI. 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. The reported median PSA values in this study was 1.42 ng/ml for normal weight men, 1.36 ng/ml for overweight men, and 0.94 ng/ml for severely obese men.

However, Ku and colleagues 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.

Other studies have not confirmed an independent effect of BMI on serum PSA levels, for example, in a cohort study by Hutterer et al[103] of more than 500 men involved in a community-based screening program for prostate cancer, no clear correlation between BMI and either the total concentration of PSA or the percentage of free PSA was found. 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)[103].

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. The mean PSA

reported in their study was 1.07 ± 0.87 ng/ml for African Americans and 1.07 ± 0.62 ng/ml for Caucasians[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. The mean PSA in their study was 1.3 ± 0.86 ng/ml[104].

In 2005, a group of investigators performed a study at each institution data on patients treated with radical prostatectomy (RP) from 1988 to 2004 in three states of the west United States. The study included 1414 patients. The study stated that, after adjusting for multiple clinicopathological characteristics, there was no significant association between BMI and preoperative PSA. There were no significant interactions between race, age and year of RP and BMI in association with PSA[101].

In addition, a group of European and Canadian authors performed a cohort study consisting of a total 630 men without known prostate cancer, who participated in an annual prostate cancer screening event, the Prostate Cancer Awareness Days (PCAD). They concluded that BMI has little if any effect on PSA distribution. In consequence, prostate cancer screening or detection strategies might be applied to obese and non-obese men using the same approach. They implied that obese men are not at lower risk of having abnormal PSA or percentage of PSA values than their non-obese counterparts. The effect of BMI may also be small in populations with low prostate cancer prevalence, such as Asian men. Conversely, it might be substantially higher in higher risk populations such as among African Americans. For example, higher intake of animal fat in African Americans may predispose to higher BMI and to a higher rate of prostate cancer. This study addressed white French-Canadians, whose gene pool may differ from English speaking Canadians or from men from the United States. It demonstrates that the lack of BMI effect may transcend several ethnic backgrounds[103].

The association between BMI and decreased PSA levels was hypothesized to be due to lower testosterone serum levels[97] or plasma hemodilution where obesity causes larger plasma volume in comparison to non-obese persons which might affect the levels of molecular markers[169].

The present study has shown an association between prostate volume and BMI of recruited subjects, meaning that the prostate volume increased with increasing BMI. This observation was also reported in multiple studies throughout the literature.

In accordance, Dahle et al[106] reported variations in prostate size with increasing degrees of obesity in 200 men with BPH in comparison to 302 controls. The authors also found an increased risk of BPH associated with increased BMI and elevated serum insulin levels. The median value for PSA for BPH patients examined in this study was 6.75 ng/ml and for controls was 1.55 ng/ml. The mean body mass index in the study was 22.3 ± 3.3 kg/m^2 for BPH patients, and 21.9 ± 3.3 kg/m^2 for controls.

Also in conjunction, Hammarsten and Hogstedt[107] reported, in a population-based study which included a total of 307 men, that obesity and high fasting insulin levels were associated with increased prostate sizes and prostate growth rates. The median annual BPH growth rate in the total group was 1.03 ml/year. The median annual BPH growth rate was

faster in men with metabolic disease, NIDDM, treated hypertension, obesity and dyslipidaemia than in men without metabolic disease.

Similarly, Freedland et al[101], in an institution-based study which included 1414 men, confirmed that increasing BMI was associated with larger prostate size. However, the authors reported that this finding was only observed in men younger than 63 years old with a BMI < 35 kg/m^2. The present study had a mean age of 60.21 ± 5.95 years, which is nearly similar to Freedland et al study, however, no obvious correlations between age and any of the study variables were reported in the present study. This can be attributed to the lower sample size of the present study in comparison to this study.

However, Loeb et al[99] did not find such an association between prostate size and obesity. The differences between the Loeb et al study and the current study can be attributed to different methodology used in both studies, where Loeb et al did not calculate BMI for the patients included and instead used height, weight and waist circumference as a reference to the degree of obesity. In addition, Loeb et al included patients scheduled for radical prostatectomy in contrast to the present study which did not include patients with a history or clinical evidence of a previously diagnosed or treated cancer prostate.

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. The relationship between obesity and increased prostate volume was hypothesized as a consequence of the hyperinsulinemic state associated with obesity[170].

The current study also reported a negative correlation between serum testosterone and BMI values. This observation has been established in several studies throughout the literature.

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].

Several mechanisms were introduced that explained this relationship including increased estrogen levels[87,118-120], polymorphism of the aromatase enzyme[121,122], endogenous opiods[123-125], sleep apnea[126-131], insulin resistance[132,171], and direct effect on testicular function[134-138].

In our study both diabetes and obesity appeared to decrease serum PSA, serum testosterone, and PSA density, also both of them appeared to increase prostate volume.

Interestingly by analyzing these data using multiple regression analysis for serum PSA, serum testosterone, PSA density, and prostate size as regarding the effect of DM & BMI on them, the DM effect was stronger than BMI effect.

The incidence of clinical prostate cancer is low in Asia, intermediate in Africa and Eastern Europe and high in Western Europe and North America[172]. The factors responsible for the differences in incidence of prostate cancer in different parts of the world remain unclear, although it is well known that prostate cancer risk and male sex hormones are strongly interrelated. Significantly higher circulating testosterone concentrations in young black men compared with young adult white men have been used to explain the differences in prostate cancer incidence between blacks and whites in the USA[171]. However, others have found no significant difference in serum testosterone levels between blacks, whites or the Japanese even though the Japanese have a very low incidence of prostate cancer[173].

Kehinde et al[96] reported a lower mean serum testosterone (12.45 nmol/l) and SHBG in Arab men compared to German men (13.4 nmol/l) which might explain the lower incidence of prostate cancer in Arab population.

In 2008, A clinical study[174] was carried out in Al Azhar University to examine the relationships between obesity, hormone profiles and semen analysis in Egyptian males. The obtained results indicated that obesity has significant negative effects on reproductive physiology and may interfere with many testicular functions. Also, it is associated with alteration in semen parameters and serum sex hormones. These results contribute additional information on the ability of obesity to reduced fertility in the Egyptian males.

The overall lower testosterone levels among Egyptian men and Arabs in general was hypothesized to be a protective factor against the development of prostate cancer as one of the factors that might be responsible for the low incidence of clinical prostate cancer in the Arab population (3 in 100,000 population)[96].

However, this hypothesis needs further elucidation through multiple, large-scale studies.

SUMMARY

Diabetes mellitus is a serious and growing health problem worldwide and is associated with severe acute and chronic complications that negatively influence both the quality of life and survival of affected individuals. The association between cancer and diabetes has been investigated extensively and most, but not all studies, found that DM is associated with an increased risk of several types of cancer. In contrast, most studies report a reduced risk of prostate cancer in men with diabetes and this most likely is attributed to the decreased testosterone levels in diabetic patients.

The study at hand aimed at finding any possible correlations between diabetes mellitus (DM) and prostate size, prostate-specific antigen (PSA) and serum testosterone in a sample of 501 Egyptian males, fulfilling the inclusion and exclusion criteria, who presented to the Main University Hospital of Alexandria university with different benign urologic problems, 207 patients were diabetics, and the other 294 patients were not diabetics. All subjects were examined and had their BMI calculated, following obtaining detailed history. PSA levels and testosterone levels were determined, fasting blood glucose (FBG) and glycosylated haemoglubin (HbA1c) in diabetic patients were determined also. Prostate size was estimated using abdominal ultrasonography.

The study at hand has shown an inverse relationship between the mean values of PSA and the DM of the recruited subjects, this finding was statistically correlated and revealed a negative strong correlation.

Additionally, the present study has shown an association between prostate volume and DM of recruited subjects.

Moreover, the current study also reported a negative correlation and an inverse relationship between serum testosterone and DM.

By the way, same results were observes with BMI, but DM effect was stronger than BMI effect.

It remains to be demonstrated whether or not decreases in serum PSA levels drive the lower risk of prostate cancer observed among diabetic men in previous studies as, if the smaller increase in serum PSA levels among diabetic men delays the diagnosis of prostate cancer, men with diabetes may be more likely to be diagnosed with later-stage disease. As such, the potential impact of diabetes on prostate-cancer detection warrants further investigation in future studies.