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Original Research Article

The negative correlation between testosterone levels and age in healthy Indonesian men residing in the special capital province of Jakarta, Indonesia

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ABSTRACT

Background: Testosterone levels in the circulation determined by production and secretion by Leydig cell in the testes. The action mechanism of testosterone to target cells mediated by sex hormone binding globulin (SHBG). The levels of testosterone and SHBG in circulation determine men's health. The objective in this study to know the relationship between testosterone, SHBG and insulin with age in healthy Indonesian men residing in the special capital province of Jakarta, Indonesia.
Methods: This study is a cross-sectional study involving 250 healthy Indonesian men residing in the special capital province of Jakarta, Indonesia. Consecutive sampling was done in this study. Testosterone, SHBG and insulin in the serum were measured by immunoradiometric assay (IRMA). Glucose, triglycerides and albumin were measured using a spectrophotometer. Regression analysis was done to know the correlation between testosterone, SHBG and insulin with age.
Results: The levels of TT, free testosterone (FT), SHBG and percentage of free testosterone (%FT) in healthy Indonesian men were negatively correlated with age ($p<0.05$). Free testosterone index (FTI) and insulin are not correlated with age ($p>0.05$). The levels of SHBG, FT, %FT and FTI were correlated positively with TT ($p<0.05$), but insulin did not correlate with TT ($p>0.05$). The %FT and FTI were positively correlated with FT ($p<0.05$), but SHBG and insulin levels did not correlate with FT ($p>0.05$). SHBG levels are not correlated with insulin ($p>0.05$). The rate of decline in TT levels in this study 9.8% per decade, while in SHBG levels 8.19% per decade.
Conclusions: The levels of TT, FT, % FT and SHBG in this study were negatively correlated with age, but the FTI and insulin did not correlate with age. The rate of decline in TT levels in this study 9.8% per decade, while in SHBG levels 8.19% per decade.

Keywords: Age, Insulin, Sex hormone binding globulin, Testosterone

INTRODUCTION

Testosterone is a steroid hormone that functions in spermatogenesis. Production of testosterone under the control of the hypothalamic-pituitary-gonadal.[1] Production of testosterone is controlled by gonadotropin releasing hormone (GnRH), luteinizing hormone (LH) and follicle stimulating hormone (FSH). Production of FSH and LH stimulated by GnRH, so the tubulus seminiferous become mature.[2,3] LH stimulates the Leydig cells to produce testosterone, while FSH stimulates the Sertoli cells to synthesize androgen binding protein (ABP).[4,5] The function of ABP as testosterone transport from the interstitial tissues toward germinal epithelial cell

through Sertoli cells. ABP also transported of testosterone to the epididymis.[6] Furthermore, FSH production play an importance role to ABP production and indirect function regulation to the epididymis and sperm motility.[7]

Testosterone intratesticular required for spermatogenesis. Testosterone excess for spermatogenesis to be secreted into the circulation system. Approximately 50% of circulating testosterone is bound to albumin, ± 44% bound to SHBG, ± 4% bound by cortisol-binding globulin (CBG), and ± 2% as free testosterone (FT). Circulating testosterone levels are often referred to as total testosterone (TT). Study result shows that TT levels in men decreases with increasing age.[8]

FT levels in the circulation plays a key role in the negative feedback on the hypothalamus-pituitary-testes. FT levels in the circulation determined by LH levels. LH levels in the circulation directly determine testosterone secretion by testes.[9] Only FT fraction that function in steroid action to target cells, including for bone and muscle growth.[10-12]

Sex hormone binding globulin (SHBG) is a plasma glycoprotein synthesized by hepatocytes and also produced by the Sertoli cells.[13,14] SHBG regulate androgen action and reversible with high affinity to androgens in circulation (DHT, testosterone, 3α-androstenediol) and estrogen with lower affinity.[13,15] In older men, increased of SHBG levels followed by decreased of FT levels, but TT levels did not change.[16] Study result shows that low levels of SHBG and testosterone in the circulation associated with metabolic syndrome.[17] The changes of SHBG levels in the circulation can be caused by metabolic syndrome, overweight/obese and smoking habits.[18-20] The other result showed that SHBG protein polymorphisms did not affect to the levels of SHBG, TT and FT.[21]

Insulin produced by pancreatic cells and necessary for carbohydrate metabolism in the cells. Furthermore, it has been proven in men that increasing testosterone levels decreases insulin sensitivity.[22] It has also been demonstrated in clinical trials that testosterone therapy decreases insulin resistance.[23] Current study shows that insulin levels affected by SHBG protein polymorphism in healthy Indonesian men.[21]

Recent research shows that the aging process results in an anabolic hormone defect, as resulting in lower physical activity and reduce the quality of nutrition.[24] There is no research data about the correlation between testosterone and SHBG levels with age in healthy Indonesian men. We also do not know how the relationship between testosterone and SHBG levels with insulin. The general objective of this study to know the circumstances of the relationship between testosterone, SHBG and insulin levels with age in healthy Indonesian men residing in the special capital province of Jakarta, Indonesia.

METHODS

This study is a cross-sectional study involving 250 healthy Indonesian men. All subjects assessed for eligibility. This study has obtained permission from the research ethics committee, faculty of medicine, university of Trisakti, Jakarta, Indonesia. All subjects gave written informed consent before following this study.

Subjects in this study are healthy Indonesian men residing in the special capital province of Jakarta (East Jakarta, North Jakarta, West Jakarta, South Jakarta or Central Jakarta), Indonesia. Sampling was done by consecutive sampling. Two hundred and fifty subjects who met the inclusion criteria. Inclusion criteria include healthy Indonesian men according to physical examination performed by a physician, 31-60 years of age, and at least one child. Blood sample collection was conducted in January-September 2013. The levels of fasting blood glucose 70-105 mg/dL, triglyceride 40-160 mg/dL, and albumin 3.5-5.3 mg/dL. Exclusion criteria include liver cirrhosis, hypergonadal, hypogonadal, diabetes, medications that affect to liver function, SHBG levels, steroid and insulin levels. Subjects were excluded if who were not present during the retrieval of research data. Data subjects were not included in the analysis if a blood sample lysis.

Fasting blood collection for all subjects was done in the morning. Ten milliliters of blood were taken from the cubital vein. Serum isolation from blood sample was done by centrifugation at 3000 revolutions per minute (rpm) for 20 minutes. Serum is stored at -20 °C. Measurement of SHBG, TT, FT, insulin, glucose, triglyceride and albumin levels in the serum was done at the Laboratory of Endocrinology, Faculty of Medicine, University of Indonesia.

Hormone levels measurement such as TT, FT, SHBG and insulin by radioimmunoassay (IRMA). Hormone levels measurement was done in duplicate. We used Coat-A-Count TT to measure TT, Coat-A-Count FT to measure FT, IRMA-Count SHBG to measure SHBG and Coat-A-Count Insulin reagents to measure insulin levels in the serum. Reagents are produced by DPC: 5210 Pacific Concourse Drive, Los Angeles, California 90045, USA). Coefficient of variation (intra-assay and inter-assay) and sensitivity in the value of acceptance criteria.

Measurement of glucose, triglyceride and albumin levels was done by enzymatic. Glucose-hexokinase reagent was used to measure glucose, while triglyceride-GPO reagent to measure triglyceride and albumin reagent was used to measure albumin. The third type of reagent made by Chiron Diagnostics GmbH, Siemens Strasse 3, D-35 463 Fernwald, Germany). Spectrophotometer SEAC CH 100 was used to measure the levels of these substances. Precision, accuracy and deviation of measurements in the value of acceptance criteria.

The %FT was calculated using the formula {(FT/TT) x 100%}, whereas the FTI was calculated using the formula {(TT/SHBG) x 100}.

Statistical analysis

Regression analysis was used to determine the relationship between age, SHBG, TT, FT, %FT, FTI and insulin.

RESULTS

Subjects in this study are 250 healthy Indonesian men, 31-60 years of age. Characteristics of the subjects are presented in Table 1.

Table 1: Characteristics of the subjects.

Variable	Mean±SD
Age (years)	46.2±8.71
BMI (kg/m^2)	22.93±4.25
Glucose (mg/dL)	90.86±8.63
Triglyceride (mg/dL)	102.01±9.26
Albumin (mg/dL)	4.30±0.12

Abbreviations: SD = standard of deviation, BMI = body mass index, kg/m2 = kilogram per meter square, mg/dL = milligrams per decilitre.

Correlation between SHBG, TT, FT, % FT, FTI and insulin with age are presented in Table 2.

Table 2: Correlations between SHBG, TT, FT, % FT, FTI and insulin with age.

	Regression equation	p value	R	R^2
SHBG (nmol/L)	= 48.849 – (0.328*age)	0.000	0.312	0.097
TT (nmol/L)	= 28.827 – (0.224*age)	0.000	0.424	0.180
FT (nmol/L)	= 0.088 – (0.001*age)	0.000	0.341	0.116
%FT (%)	= 0.275 + (0.002*age)	0.027	0.190	0.036
FTI	= 62.117 – (0.105*age)	0.483	0.061	0.055
Insulin (µIU/mL)	= 7.994 – (0.018*age)	0.492	0.060	0.004
SHBG (nmol/L)	= 18.988 + (0.802*TT)	0.000	0.404	0.163
FT (nmol/L)	= 0.036 + (0.001*TT)	0.000	0.505	0.255
%FT (%)	= 0.560 + (0.011*TT)	0.000	0.621	0.386
FTI	= 27.409 + (1.607*TT)	0.000	0.495	0.245
Insulin (µIU/mL)	= 8.942 – (0.094*TT)	0.052	0.168	0.028
SHBG (nmol/L)	= 27.955 + (93.905*FT)	0.113	0.138	0.019
%FT (%)	= 0.228 + (2.002*FT)	0.000	0.331	0.110
FTI	= 33.775 + (369.639*FT)	0.000	0.332	0.110
Insulin (µIU/mL)	= 8.700 – (23.715*FT)	0.156	0.123	0.015
SHBG (nmol/L)	= 36.633 – (0.374*INS)	0.225	0.105	0.011

Abbreviations: SHBG = sex hormone binding globulin, TT = total testosterone, FT = free testosterone; %FT = the percentage of free testosterone, FTI = free testosterone index. nmol/L = nano mol per liter, µIU/mL = micron international units per millilitre.

SHBG, TT, FT and %FT levels were negatively correlated with age ($p<0.05$), whereas FTI and insulin levels were not correlated with age ($p>0.05$). SHBG, FT, %FT and FTI levels were positively correlated with TT ($p<0.05$), whereas insulin levels did not correlate with TT ($p>0.05$). The %FT and FTI were positively correlated with FT ($p<0.05$), whereas SHBG and insulin were not correlate with FT ($p>0.05$). The levels of SHBG are not correlated with insulin ($p>0.05$).

DISCUSSION

Referring to normal value of TT levels used by Kapoor et al, i.e. 8.3-41.6 nmol/L, then the average of TT levels in this study 18.63±0.81 nmol/L (Mean±SD) was normal.[25] Other researchers used normal value of the TT levels 8.8-31.2 nmol/L.[26] The other result of my study in normal SHBG phenotype showed that TT levels 18.80±5.64 nmol/L, while in variant SHBG phenotype 20.31±6.86 nmol/L.[21] Moreover, study of European men showed that average of TT levels 15.8 nmol/L (95% CI: 15.2-16.3 nmol/L).[20] Based on the data, the average of TT levels in European men was lower than Indonesian men. The differences in the TT levels due to ethnic variation, dietary intake and lifestyle.[27]

According to the guidelines used by Baisley et al, the average levels of FT in this study 0.063 ± 0.0013 nmol/L is included in the range of normal values.[28] The other result of my study in normal SHBG phenotype showed that FT levels 0.065±0.01 nmol/L, while in variant SHBG phenotype 0.064±0.77 nmol/L.[21] The results of this study

indicate that the decrease in TT levels followed by a decrease in FT levels, so FT correlates positively with TT. The fact is understandable because the level of FT depends on the production of TT. It is also known that FT has the function of negative feedback and autoregulation to hypothalamus and pituitary.[29] We know that negative feedback mechanism is an important regulation of hormone levels in the circulation.

This study shows that the levels of TT and FT were negatively correlated with age. The other study also obtained the same results with this study that increasing age was followed by a decrease in the levels of TT.[17,30] The negative correlation between FT and age also obtained the same results earlier.[31,32] Compared to Canadian men, the decrease of TT levels in this study was lower. Decreases of TT levels in Canadian men 10-17% per decade, whereas in this study only 9.8% per decade.[33] Results of another study showed that decreases of TT levels in European men only 2.15% per decade.[22]

Results of this study are also consistent with other studies showing that TT levels in adult men is higher than in older men.[34] This further reinforces the fact that the increasing age decreases the levels of TT. Further research in Australia showed that men 70-89 years of age had an average level of TT 15.4 ± 5.6 nmol/L (444 ± 162 ng/dL) was lower than Australian men less than 70 years of age. In addition, the Australian men ≥70 years of age had a level were low, but still within the range of normal values.[23]

Changes in TT levels have been shown by previous researchers.[16,35] The previous study showed that in Australian men 70-89 years of age decrease in TB levels, but TT levels did not change and SHBG levels increased.[16] The difference of changes in the levels of TT and FT in this study compared to the study in Australia were caused by differences in the age of the respondent. There are other possibilities that cause these differences, for example smoking habits conducted by the respondent. We cannot control to this habit. Study of the smoking effect on FT levels was done in 7 European countries. The result showed that the levels of FT among smokers was higher than non-smokers.[20] Recent studies in men also shown that testosterone levels in smokers was higher than non-smokers.[36] These results are also consistent with studies showing the variation of FT levels in healthy adult males.[37]

The average levels of SHBG in this study 34.01±1.53 nmol/L. Based on the normal value of SHBG levels are used as guidelines by Lopez et al, the levels of SHBG in this study are included in the range of normal values.[30] SHBG levels in this study correlated negatively with age. The other result of my study showed that SHBG levels in normal SHBG phenotype 31.70±13.78 nmol/L, while in variant SHBG phenotype 37.69±16.17 nmol/L.[21] Research conducted by Lapauw et al, also obtained comparable results with this study.[31] The results of another study in Brazil showed that SHBG levels correlated positively with age. Differences on these results dues to differences in the age of the subject. The age of the subjects in this study 31-60 years, while in Brasilia 50-80 years. In Brazilian men 50-80 years of age showed increased levels of SHBG every decade.[30] Present study results suggest that SHBG levels decreased 8.19% every decade.

Result in this study shown that SHBG levels correlated positively with TT, but not correlated with FT. The positive correlation between SHBG with TT in accordance with the results of previous studies.[16] Our data suggest that SHBG synthesis by hepatocytes in syncrone with the production of testosterone by the Leydig cells. We found a positive correlation between SHBG and TT in healthy Indonesian men determined by the levels of glucose, triglyceride and albumin in the circulation. Results of other studies on diabetic men showed that TT and SHBG levels are low.[38] The other study showed that low TT levels result in high fasting blood glucose levels.[39] It also has been demonstrated a positive correlation between SHBG and TT. In diabetic men, the first year has a TT and SHBG levels was lower than normal men, but in older men who have diabetes increased TT and SHBG levels. This result caused by decrease in the availability of testosterone (bioavailable testosterone = BioT).[40] Furthermore, results of other studies on obese men showed that the decline in testicular function so that the TT and SHBG levels decreased, resulting effect on spermatogenesis. Many factors affect the levels of testosterone and SHBG. TT and SHBG had a significant negative correlation with fasting blood glucose level.[39] Results of other studies also showed that the levels of TT were lower in men with metabolic syndrome, but the levels of FT and SHBG were not different between men with metabolic syndrome compared to normal men.[41] In the front has been stated that TT levels among others influenced by nutritional factors.[27] In addition, it has been shown that nutritional factors also affected to SHBG levels in men and women.[42,43]

The average of FTI in this study 54.78. Based on the guidelines used by Ly and Handelsman, FTI in this study are included in the range of normal values.[44] FTI in this study did not correlate with age. Based on these data can be presumed that the bond between testosterone and SHBG are normal. Results of another study in men 50-80 years of age showed a decline FTI every decade.[30]

The average of %FT in this study 0.34%. Results of this study showed that the %FT within the range of normal values and positively correlated with age. The %FT is also positively correlated to TT and FT. The %FT in this study 0.35 ± 0.01%. The result study by Ronde et al, showed that the %FT 1.09 to 3.09, thus higher than the results of this study. The other result of study showed that the %FT 0.86-1.91%, thus higher than in this study.[45,46]

Insulin levels in this study 7.18±0.39 µIU/mL. Guidelines for the normal value of fasting insulin levels 6-27 µIU/mL.[47] Based on the guidelines used by the level of insulin in this study are included in the range of normal values. In this study, insulin levels did not correlate with age. Insulin also not correlated with TT, FT and SHBG. The other hand showed that insulin levels in men with variant SHBG phenotype was higher than normal SHBG phenotype.[21] This fact reinforces that genetic factors affect to insulin levels in the circulation. This is a limitation of the study because it was not done phenotyping of SHBG. Futhermore, in the pathological conditions, insulin resistance in men negatively correlated with testosterone.[48-51] The different results proved that bioavailable testosterone, TT, FT and SHBG were positively correlated with fasting insulin.[49] The results of another study showed that insulin secretion, insulin clearance and interaction of insulin with target cells defective in further age.[52]

CONCLUSION

Base on this data we concluded that the levels of TT, FT and SHBG were negatively correlated with age, but the %FT positively correlated with age, while FTI and insulin are not correlated with age. TT levels positively correlated with SHBG, FT, %FT and FTI, but not correlated with insulin. The levels of FT positively correlated with FTI and %FT, but not correlated with SHBG and insulin. The levels of SHBG are not correlated with insulin. The rate of decrease in TT levels in this study 9.8% per decade, while in SHBG levels 8.19% per decade.

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