

Varicocele may not have a chronic low-grade inflammatory background on vascular endothelium

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Abstract

Background: There is not enough finding about effects of metabolic parameters on varicocele in the literature.

Methods: Consecutive patients with a surgical repair history of varicocele were collected into the first, and age-matched control cases were collected into the second, groups.

Results: The study included 31 patients with varicocele and 80 control cases, totally. Mean age of varicocele patients was 37.0 years. Interestingly, 77.4% of the varicoceles were on the left side and 9.6% of them were on the right side ($p < 0.05$), and 12.9% of them were found bilaterally. When we compared the two groups according to mean weight, height, body mass index, triglyceride, and low density lipoproteins and prevalences of smoking, white coat hypertension, hypertension, diabetes mellitus, and coronary artery disease, there was not any significant difference according to any metabolic parameter in between ($p > 0.05$ for all).

Conclusion: Although the metabolic syndrome is a chronic low-grade inflammatory process on vascular endothelium, terminating with an accelerated atherosclerosis, end-organ failure, early aging, and premature death, varicocele may not have a chronic low-grade inflammatory background on vascular endothelium in general. On the other hand, thalasseмии and other causes of splenomegaly may cause torsion of the left renal vein and prevent its drainage. So drainage problems at the level of left renal vein due to the stronger arterial walls that cannot be obstructed easily may explain the higher prevalence of varicocele and renal atrophy on the left side in the literature since the left testicular vein drains into the left renal vein.

Key words: Varicocele, endothelial inflammation, metabolic syndrome, body mass index

Introduction

Due to the prolonged survival of human beings, systemic atherosclerosis may be the major health problem in this century, and its association with sedentary lifestyle, excess weight, smoking, and alcohol is collected under the heading of metabolic syndrome (1, 2). The syndrome is characterized by a chronic low-grade inflammatory process on vascular endothelium in the whole body (3). The inflammatory process is particularly accelerated by some factors including physical inactivity, excess weight, smoking, alcohol, chronic inflammation and infections, and cancers (4, 5). The syndrome can be slowed down with appropriate nonpharmaceutical approaches including lifestyle changes, diet, exercise, cessation of smoking, and withdrawal of alcohol (6). The syndrome contains reversible indicators including overweight, white coat hypertension (WCH), impaired fasting glucose, impaired glucose tolerance, hyperlipoproteinemias, alcohol, and smoking for the development of irreversible consequences including obesity, hypertension (HT), type 2 diabetes mellitus (DM), chronic obstructive pulmonary disease, cirrhosis, chronic renal disease, peripheral artery disease, coronary artery disease (CAD), and stroke (7, 8). In another perspective, the metabolic syndrome may be the most significant disease of human beings decreasing quality and duration of human lifespan at the moment. The syndrome induced accelerated atherosclerotic process in the whole body may be the leading cause of end-organ failure, early aging, and premature death for both genders. For example, CAD is the leading cause of death in developed countries. On the other hand, varicocele is a dilatation of pampiniform venous plexus within the scrotal sac (9-12). It occurs in 15-20% of males and 40% of infertile males, since researchers documented a recurrent pattern of low sperm count, poor motility, and predominance of abnormal sperm forms in varicocele cases (13-15). We tried to understand whether or not there are some significant relationships between metabolic parameters and varicocele in the present study.

Material and methods

The study was performed in the Internal Medicine Polyclinic of the Mustafa Kemal University between March 2007 and December 2009. Consecutive patients with a surgical repair history of varicocele were collected into the first, and age-matched control cases were collected into the second, groups. Their medical histories including smoking habit, HT, DM, CAD, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglyceride, low density lipoproteins (LDL), and an electrocardiography was performed. Current daily smokers at least for the last six months, and cases with a history of five pack-years were accepted as smokers. Insulin using diabetics and patients with devastating illnesses including malignancies, acute or chronic renal failure, chronic liver disease, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Body mass index (BMI) of each individual was calculated by the measurements of the same internist

instead of verbal expressions. Weight in kilograms is divided by height in meters squared (16). Office blood pressure (OBP) was checked after a 5 minute rest in seated position with the mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10 day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked hypertension after a 10 minutes of education about proper blood pressure (BP) measurement techniques (17). The education included recommendation of upper arm while discouraging wrist and finger devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5 minutes in the seated position before measurement. A 24 hour ambulatory blood pressure monitoring was not required due to its equal effectiveness with HBP measurements (8). Eventually, HT is defined as a BP of 135/85 mmHg or greater on HBP measurements (17). WCH is defined as OBP of 140/90 mmHg or greater, but mean HBP of lower than 135/85 mmHg, and masked HT as OBP of lower than 140/90 mmHg, but mean HBP of 135/85 mmHg or greater (17). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 100 and 125 mg/dL, and diagnosis of cases with a 2 hour plasma glucose level of 200 mg/dL or higher is DM (16). A stress electrocardiography was performed in suspected cases, and a coronary angiography was obtained only for the stress electrocardiography positive cases. Eventually, mean weight, height, BMI, triglyceride, and LDL values and prevalence of smoking, WCH, HT, DM, and CAD were detected in each group, and results were compared in between. Mann-Whitney U Test, Independent-Samples T Test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 31 patients with varicocele and 80 control cases, totally. Mean age of varicocele patients was 37.0 years. Interestingly, 77.4% of the varicoceles were on the left side and only 9.6% of them were on the right side ($p < 0.05$), and 12.9% of them were found, bilaterally. When we compared the two groups according to mean weight, height, BMI, triglyceride, and LDL values and prevalence of smoking, WCH, HT, DM, and CAD, there was not any statistically significant difference according to any metabolic parameter in between ($p > 0.05$ for all) (Table 1 - next page).

Table 1: Characteristic features of the study cases

Variables	Cases with varicocele	p-value	Control cases
Number	31		80
Mean age (year)	37.0 ± 12.5 (18-75)	Ns*	38.1 ± 11.1 (19-75)
Prevalence of smoking	61.2% (19)	Ns	52.5% (42)
Mean weight (kg)	80.0 ± 14.6 (51-99)	Ns	79.5 ± 12.8 (52-111)
Mean height (cm)	175.0 ± 7.2 (152-187)	Ns	173.5 ± 7.2 (158-195)
Mean BMI† (kg/m ²)	26.0 ± 4.2 (16.6-33.5)	Ns	26.3 ± 4.0 (18.0-39.2)
Mean triglyceride (mg/dL)	131.0 ± 77.3 (63-332)	Ns	164.0 ± 81.7 (51-385)
Mean LDL‡ (mg/dL)	127.8 ± 36.1 (66-198)	Ns	125.8 ± 34.9 (63-208)
Prevalence of WCH§	35.4%	Ns	31.2%
Prevalence of HT	3.2%	Ns	1.2%
Prevalence of DM¶	0.0%	Ns	3.7%
Prevalence of CAD**	3.2%	Ns	0.0%

*Nonsignificant (p>0.05) †Body mass index ‡Low density lipoproteins §White coat hypertension ||Hypertension ¶Diabetes mellitus **Coronary artery disease

Discussion

Probably obesity is found among one of the irreversible endpoints of the metabolic syndrome, since after development of obesity, nonpharmaceutical approaches provide limited benefit either to heal obesity or to prevent its complications. Overweight and obesity probably lead to a chronic low-grade inflammation on vascular endothelium that is associated with many coagulation and fibrinolytic abnormalities suggesting that excess weight may cause a prothrombotic and proinflammatory state all over the body (18). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (19, 20). Elevation of C-reactive protein (CRP) levels in serum carries predictive power for the development of atherosclerotic end-points (21, 22), and overweight and obesity are considered as strong factors for controlling of CRP concentration in serum, because adipose tissue produces biologically active leptin, tumor necrosis factor- α , plasminogen activator inhibitor-1, and adiponectin. So adipose tissue is involved in the regulation of cytokines, and individuals with overweight and obesity have increased CRP levels in serum (23, 24). On the other hand, individuals with excess weight will have an increased circulating blood volume as well as an increased cardiac output, thought to be the result of increased oxygen need of the extra tissue. The prolonged increase in circulating blood volume may cause myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of atherosclerosis and HT. In addition to atherosclerosis and HT, FPG and total cholesterol levels

in serum were elevated parallel to the increased BMI values (25). Similarly, prevalence of CAD and ischemic stroke increased parallel to increased BMI values in another study (26). On the other hand, the chronic low-grade inflammatory process may also cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (27). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increased throughout the range of moderate to severe weight excess for both genders in all age groups (28).

Testes are paired male genital organs located in the scrotal sac. They contain sperm, spermatogonia (sperm producing cells), Sertoli cells (sperm nourishing cells), and Leydig cells (testosterone producing cells). Epididymis is a small tubular structure attached to the testes that serves as a storage reservoir wherein sperm mature. Sperm travel through the vas deferens, which connects epididymis to the prostate gland. Spermatocord contains vas deferens, arteries, and veins that are also called pampiniform venous plexus, nerves, and lymphatics. Pampiniform venous plexus drains blood from testes, epididymis, and vas deferens, and eventually become spermatic veins that drain into the main circulation of kidneys. Pampiniform venous plexus may become tortuous and dilated, like varicose veins of legs. So a scrotal varicocele is simply a varicose dilatation of the pampiniform plexus above and around the testicle. As also detected in the present study, varicoceles are much more common on the left side (nearly 80% to 90%) due to several anatomic factors including angle at which the left testicular vein enters the left renal vein, lack of effective

antireflux valves at the juncture of left testicular vein and left renal vein, the nutcracker syndrome, and some other left renal vein anomalies such as passage behind the aorta (29, 30). The nutcracker syndrome results mostly from the compression of the left renal vein between the abdominal aorta and superior mesenteric artery, although some other variants exist (31). But according to our opinion, the higher prevalence of varicocele on the left side may mainly be a result of high prevalence of thalassemia minor and other causes of splenomegaly in the population that may cause drainage problems at the level of left renal vein.

The accelerated atherosclerotic process can also affect the renal arteries, and may lead to poor perfusion of the kidneys leading to renal failure. The right renal artery is longer than the left because of the location of the aorta. Additionally, the right renal artery is lower than the left because of the position of the right kidney. So the left kidney possibly has a relatively higher arterial pressure due to the shorter distance to the heart as an underlying cause of endothelial damage and atherosclerosis. But according to our opinion, the accelerated atherosclerotic process alone cannot explain the significantly higher prevalence of renal atrophy on the left side in the literature (1.3% versus 0.2%, $p < 0.001$) (32). On the other hand, the high prevalence of associated thalassemias (30.3%) and splenomegaly (51.5%) with the left renal atrophy cases may be important for the explanation (32), since spleen and left kidney are closely related organs which may also be observed with the development of varicose veins from the left renal vein at the splenic hilus in cirrhotic patients. Any pressure on the left kidney as in splenomegaly cases, may cause torsion of the left renal vein, and prevents its drainage. We especially think about the drainage problems at the level of left renal vein due to the stronger arterial walls that cannot be obstructed easily and the higher prevalences of both renal atrophy and varicocele on the left side in the literature (11, 32).

A patient with varicocele is usually asymptomatic and often seeks an evaluation for infertility after failed attempts at conception. An untreated varicocele, especially if large enough, may cause long-term deterioration in sperm and even testosterone production. But presence of a varicocele does not mean that surgical repair is always required. Young men with varicocele but normal ipsilateral testicular volume should be offered follow-up monitoring with annual objective measurements of testicular volume and semen analyses, since one-sided varicoceles can often affect the opposite testicle (9-12). A previous study suggested that up to 80% of men with a left clinical varicocele had bilateral varicoceles revealed by noninvasive radiologic testing (33). Similarly, 16% of varicoceles in patients with infertility were reported with bilateral occurrence in all of them (15). Reasons for surgical repair include testicular pain unresponsive to symptomatic treatment, testicular atrophy (volume less than 20 mL or length less than 4 cm), and unexplained infertility in males. If an infertile male has bilateral varicoceles, both should be repaired since scrotal varicoceles may be the most common cause of poor sperm production and decreased semen quality.

But how varicoceles impair sperm structure, function, and production is unknown. Although an increased heat effect caused by impaired circulation appears to be the most reproducible defect, the possible effects of pressure, oxygen deprivation, and toxins may also be responsible. But regardless of the mechanism of action, varicoceles are a significant factor in decreasing testicular function and reducing semen quality in a large percentage of infertile men.

As a conclusion, although the metabolic syndrome is a chronic low-grade inflammatory process on vascular endothelium, terminating with an accelerated atherosclerosis, end-organ failure, early aging, and premature death, varicocele may not have a chronic low-grade inflammatory background on vascular endothelium in general. On the other hand, thalassemias and other causes of splenomegaly may cause torsion of the left renal vein and prevent its drainage. So drainage problems at the level of left renal vein due to the stronger arterial walls that cannot be obstructed easily, may explain the higher prevalence of varicocele and renal atrophy on the left side in the literature since the left testicular vein drains into the left renal vein.

References

1. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; 365: 1415-1428.
2. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109: 433-438.
3. Tonkin AM. The metabolic syndrome(s)? *Curr Atheroscler Rep* 2004; 6: 165-166.
4. Helvacı MR, Kaya H, Seyhanlı M, Cosar E. White coat hypertension is associated with a greater all-cause mortality. *J Health Sci* 2007; 53: 156-160.
5. Helvacı MR, Kaya H, Duru M, Yalcin A. What is the relationship between white coat hypertension and dyslipidemia? *Int Heart J* 2008; 49: 87-93.
6. Helvacı MR, Aydin LY, Aydin Y. Chronic obstructive pulmonary disease may be one of the terminal end points of metabolic syndrome. *Pak J Med Sci* 2012; 28: 376-379.
7. Helvacı MR, Kaya H, Gundogdu M. Gender differences in coronary heart disease in Turkey. *Pak J Med Sci* 2012; 28: 40-44.
8. Helvacı MR, Seyhanlı M. What a high prevalence of white coat hypertension in society! *Intern Med* 2006; 45: 671-674.
9. Weiss AJ, Kellman GM, Middleton WD, Kirkemo A. Intratesticular varicocele: sonographic findings in two patients. *Am J Roentgenol* 1992; 158: 1061-1063.
10. Simmons MZ, Wachsberg RH, Levine CD, Spiegel N. Intra-testicular varicocele: gray-scale and Doppler ultrasound findings. *J Clin Ultrasound* 1996; 24: 371-374.

11. Ozcan H, Aytac S, Yagci C, Turkolmez K, Kosar A, Erden I. Color Doppler ultrasonographic findings in intratesticular varicocele. *J Clin Ultrasound* 1997; 25: 325-329.
12. Mehta AL, Dogra VS. Intratesticular varicocele. *J Clin Ultrasound* 1998; 26: 49-51.
13. O'Donnell PG, Dewbury KC. The ultrasound appearances of intratesticular varicocele. *Br J Radiol* 1998; 71: 324-325.
14. Morvay Z, Nagy E. The diagnosis and treatment of intratesticular varicocele. *Cardiovasc Intervent Radiol* 1998; 21: 76-78.
15. Das KM, Prasad K, Szmigielski W, Noorani N. Intratesticular varicocele: evaluation using conventional and Doppler sonography. *Am J Roentgenol* 1999; 173: 1079-1083.
16. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106: 3143-3421.
17. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; 21: 821-848.
18. De Pergola G, Pannacciulli N. Coagulation and fibrinolysis abnormalities in obesity. *J Endocrinol Invest* 2002; 25: 899-904.
19. Ross R. Atherosclerosis: An inflammatory disease. *N Engl J Med* 1999; 340: 115-126.
20. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* 2001; 103: 1813-1818.
21. Ridker PM. High-sensitivity C-reactive protein and cardiovascular risk: rationale for screening and primary prevention. *Am J Cardiol* 2003; 92: 17-22.
22. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998; 279: 1477-1482.
23. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999; 282: 2131-2135.
24. Funahashi T, Nakamura T, Shimomura I, Maeda K, Kuriyama H, Takahashi M, et al. Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. *Intern Med* 1999; 38: 202-206.
25. Zhou B, Wu Y, Yang J, Li Y, Zhang H, Zhao L. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. *Obes Rev* 2002; 3: 147-156.
26. Zhou BF. Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases - report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. *Biomed Environ Sci* 2002; 15: 245-252.
27. Helvacı MR, Aydin Y, Gundogdu M. Smoking induced atherosclerosis in cancers. *HealthMED* 2012; 6: 3744-3749.
28. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999; 341: 1097-1105.
29. Little AF, Lavoipierre AM. Unusual clinical manifestations of the Nutcracker Syndrome. *Australas Radiol* 2002; 46: 197-200.
30. Mohammadi A, Ghasemi-Rad M, Mladkova N, Masudi S. Varicocele and nutcracker syndrome: sonographic findings. *J Ultrasound Med* 2010; 29: 1153-1160.
31. Kurklinsky AK, Rooke TW. Nutcracker phenomenon and nutcracker syndrome. *Mayo Clin Proc* 2010; 85: 552-559.
32. Davran R, Helvacı MR, Davarci M. Left renal atrophy. *Int J Clin Exp Med* 2014; 7: 1603-1606.
33. Gat Y, Bachar GN, Zukerman Z, Belenky A, Gornish M. Varicocele: a bilateral disease. *Fertil Steril* 2004; 81: 424-429.