OBESITY MAY ACTUALLY BE A PRECIRRHOTIC CONDITION IN ADULTS

Mehmet Rami Helvaci (1)
Engin Altintas (1)
Mustafa Yaprak (1)
Ramazan Davran (2)
Abdulrazak Abyad (3)
Lesley Pocock (4)

(1) Specialist of Internal Medicine, M.D.
(2) Specialist of Radiology, M.D.
(3) Middle-East Academy for Medicine of Aging, M.D.
(4) Medi-WORLD International

Corresponding Author:
Mehmet Rami Helvaci, M.D.
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

Received: March 2022; Accepted: April 2022; Published: May, 2022
Citation: Mehmet Rami Helvaci et al. Obesity may actually be a precirrhotic condition in adults. Middle East Journal of Nursing 2022; 16(1): 20-26 DOI: 10.5742/MEJN2022.9378017

Abstract

Background: There may be some significant relationships between the umbilical hernia, obesity, and cirrhosis during the process of metabolic syndrome in adults.

Method: Consecutive patients with an umbilical hernia and/or a surgical repair history of the umbilical hernia were included.

Results: There are 46 patients with the umbilical hernia with a mean age of 62.0 years, and 73.9% of them were female. Body mass index was higher in the hernia patients (33.6 versus 29.1 kg/m2, p= 0.000). Although the prevalence of hypertension (HT) was also higher in the hernia group (50.0% versus 27.3%, p<0.01), mean values of triglycerides and low density lipoproteins and prevalence of white coat hypertension (WCH) were lower in them (p<0.05 for all). Although prevalences of diabetes mellitus (DM) and coronary heart disease (CHD) were also higher in the hernia patients, the differences were nonsignificant, probably due to the small sample size of the hernia group.

Conclusion: There may be some significant relationships between the umbilical hernia, obesity, cirrhosis, and other endpoints of the metabolic syndrome including HT, DM, and CHD, probably on the bases of prolonged inflammatory, atherosclerotic, and pressure effects of excessive fat tissue on abdominal wall muscles. The inverse relationships between obesity and hypertriglyceridemia and hyperbetalipoproteinemia may be explained by the hepatic fat accumulation, inflammation, and fibrosis induced relatively lost hepatic functions in obesity. Similarly, the inverse relationship between obesity and WCH may be explained by progression of WCH into overt HT in obesity. So obesity may actually be a precirrhotic condition in adults.

Key words: Obesity, cirrhosis, metabolic syndrome, umbilical hernia, hepatosteatosis, atherosclerosis, end-organ insufficiency

Introduction

The endothelium is a monolayer of endothelial cells which constitutes the inner cellular lining of artery, vein, capillary, and lymphatics. It is the major player in the control of blood fluidity, platelets aggregation, and vascular tone. It may be the major actor in immunology, inflammation, and angiogenesis. It may also be important in the endocrinology. The endotelial cells control vascular tone and blood flow by synthesizing and releasing nitric oxide, metabolites of arachidonic acid, and reactive oxygen species. Additionally, they are also important for generation of vasoactive hormones such as angiotensin II. An endothelial dysfunction linked to an imbalance in the synthesis and/or release of these endothelial factors may explain the initiation of several cardiovascular pathologies including hypertension (HT) and atherosclerosis. On the other hand, chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human being (1, 2). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, excess weight, animal-rich diet, smoking, alcohol, chronic inflammations, and prolonged infections for the development of terminal consequences including obesity, HT, type 2 diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, end-organ insufficiencies, cancers, early aging, and premature death (3, 4). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, cancers, and aging, endothelial changes can not be reversed completely due to their fibrotic natures (5, 6). The accelerating factors and terminal endpoints are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (7, 8). On the other hand, there may be some significant relationships between the umbilical hernia, obesity, and cirrhosis during the process of metabolic syndrome in adults.

Material and methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and January 2010. Consecutive patients with an umbilical hernia and/or a surgical repair history of the umbilical hernia were collected in the first, and age and sex-matched controls were collected into the second groups. Their medical histories including smoking habit, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglycerides, 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, chronic renal failure, decompensated cirrhosis, uncontrolled hyper- or hypothyroidism, and congestive heart failure were excluded to avoid their possible effects on weight. Body mass index (BMI) of each case was calculated by the measurements of the Same Clinician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (9). Office blood pressure (OBP) was checked after a five-minute of rest in seated position with the mercury sphygmomanometer on three visits, and no smoking was permitted during the previous two-hour. 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-minute education about proper BP measurement techniques (10). A 24-hour ambulatory blood pressure monitoring (ABP) was not required due to its equal effectiveness with HBP measurements (11). Eventually, HT is defined as a BP of 135/85 mmHg or greater on HBP measurements (10). White coat hypertension (WCH) is defined as an OBP of 140/90 mmHg or greater but mean HBP of lower than 135/85 mmHg, and masked HT as an OBP of lower than 140/90 mmHg but mean HBP of 135/85 mmHg or greater (10). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already taking 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 two-hour plasma glucose level of 200 mg/dL or higher is DM (9). 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, triglycerides, and LDL values and prevalences of smoking, WCH, HT, DM, and CHD 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 46 patients in the umbilical hernia and 84 cases in the control groups. Mean age of the umbilical hernia patients was 62.0 years, and 73.9% of them were female. Prevalence of smoking was lower in the umbilical hernia group, nonsignificantly (13.0% versus 19.0%, p>0.05). Although the mean heights of the two groups were similar (157.4 versus 158.7 cm, p>0.05), the umbilical hernia patients were heavier than the control cases, significantly (85.1 versus 73.1 kg, p= 0.001). As a result, the BMI was also higher in the umbilical hernia patients, significantly (33.6 versus 29.1 kg/m2, p= 0.000). Interestingly, although the significantly higher mean weight and BMI of the patients with the umbilical hernia, the mean triglycerides and LDL values and prevalence of WCH were significantly lower in them (p<0.05 for all). On the other hand, prevalence of HT was significantly higher in the umbilical hernia group (50.0% versus 27.3%, p<0.01). Although the prevalences of DM and CHD were also higher in the umbilical hernia group, the differences were nonsignificant, probably due to the small size of the umbilical hernia group (Table 1).

Table 1: Characteristic features of the study cases

Variables	Cases with umbilical hernia	*p*-value	Control cases
Number	46		84
Female ratio	*73.9%*	Ns*	73.8%
Mean age (year)	*62.0 ± 13.2 (29-82)*	Ns	62.2 ±13.0 (29-83)
Prevalence of smoking	13.0%	Ns	19.0%
Mean weight (kg)	*85.1 ± 20.8 (54-172)*	*0.001*	73.1 ±13.1 (44-104)
Mean height (cm)	157.4 ±11.2 (134-191)	Ns	158.7 ±10.0 (138-181)
Mean BMI† (kg/m2)	*33.6 ± 5.7 (21.0-47.1)*	*0.000*	29.1 ±5.4 (17.2-42.9)
Mean triglycerides (mg/dL)	119.6 ±69.2 (49-361)	*0.041*	*145.9 ± 76.9 (56-394)*
Mean LDL‡(mg/dL)	120.2 ±35.5 (49-193)	*0.042*	*138.0 ± 42.1 (10-239)*
Prevalence of WCH§	23.9%	*<0.05*	*41.6%*
Prevalence of overt HT‖	*50.0%*	*<0.01*	27.3%
Prevalence of DM¶	*30.4%*	Ns	28.5%
*Prevalence of CHD***	*17.3%*	Ns	13.0%

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

Discussion

The umbilical hernias are frequent anomalies of the abdominal wall muscles in both genders. Most of the umbilical hernias have an acquired origin, and only 10% of them have congenital causes in adults (12). They are more common in women both in children and adults (13). They are more common under the age of four and over the age of 50 years with unknown reasons, yet (13). They are especially common in premature babies (up to 84%), overweight children, and middle-aged multiparous women. According to the literature, their prevalences are around 2% in adults. As also observed in the present study, the umbilical hernias are frequently seen with terminal endpoints of the metabolic syndrome including obesity, HT, DM, cirrhosis, CHD, PAD, COPD, CRD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and cancers. There are not big differences in the frequency between the various ethnic groups in adults, supporting the possible acquired etiologies such as the metabolic syndrome (13). The umbilical hernias occur when a part of the intestine protrudes through a weak spot in the abdominal wall muscles at the site of umbilicus. Babies are prone to this malformation due to the process of fetal development during which abdominal organs develop outside the abdominal cavity, and then, they come into the abdominal cavity through an opening which will become the umbilicus later. Importantly, the umbilical hernias must be distinguished from paraumbilical ones, defects in one side of the midline at the umbilical region in adults, and from omphaloceles in newborns. Most umbilical hernias close on their own by the age of one year, although up to 10% may take longer to heal in infants. To prevent complications, the umbilical hernias those do not disappear by the age of four years or those appear during adulthood may need surgical repair operations. The umbilical hernias may become incarcerated or strangulated, but the risk is low, since the underlying defect of the abdominal wall muscles is larger than found in the inguinal ones. The risk of incarceration is half of the inguinal hernias, but three times higher than the femoral ones in the previous study (14). Up to 90% of incarcerated hernias of umbilicus occur in women with a mortality rate up to 25% (14). There is also a higher risk of incarceration in the cirrhotics receiving medical treatment for ascites, carrying an implant of a peritoneo-venous shunt, or getting an evacuating paracentesis (15). The higher prevalence of umbilical hernias in cirrhosis may also support the pressure effect of intra-abdominal fluid on abdominal wall muscles (16). Obesity, pregnancy, ascites, and peritoneal dialysis induced distensions of the abdominal wall may cause pulling of the muscles and deterioration of connective tissue over the umbilicus. The frequent association of the umbilical hernias with other abdominal wall defects may also support the possible etiologic role of the biophysical changes (13). In the previous study of umbilical hernias, 42% of them were associated with another hernia, and 5% of them were associated with more than two hernias (13). Abnormal dispositions of the umbilical fascia may be one of the factors contributing to herniations (17). Tendinous fibers coming from the muscles of both sides of the abdominal wall decussate obliquely at the linea alba, acquiring different levels of complexity (18). Simpler decussations may be found in cases with umbilical hernias in which the sac protrudes at the midline. Obesity, pregnancy, ascites, and peritoneal dialysis induced excess pressure on abdominal wall muscles may facilitate rupture of the fibers which decussate in a simple fashion at the linea alba on the umbilicus. In contrast, patients with more complex (triple) decussations may present with paraumbilical hernias in the above conditions. On the other hand, recanalized umbilical veins and deterioration of connective tissue secondary to the accelerated atherosclerotic process of the metabolic syndrome may also facilitate the herniations in cirrhosis.

Obesity may be one of the major terminal endpoints of the metabolic syndrome, since after development of obesity, nonpharmaceutical approaches provide limited benefit either to improve obesity or to prevent its complications. Overweight and obesity probably lead to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess weight in all age groups (19). The low-grade chronic inflammation 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 (20). Overweight and obesity are associated with many coagulation and fibrinolytic abnormalities suggesting that they cause a prothrombotic and proinflammatory state (21). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (22, 23). For example, elevated C-reactive protein (CRP) levels in serum carry predictive power for the development of major cardiovascular events (24, 25). Overweight and obesity are considered as strong factors for controlling of CRP concentration in serum, since adipose tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (26, 27). 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 demand of the excessive fat tissue. The prolonged increase in circulating blood volume may lead to myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of atherosclerosis and HT. In addition to systemic atherosclerosis and HT, FPG and serum cholesterol increased and high density lipoproteins decreased with increased BMI (28). Similarly, the prevalences of CHD and stroke, particularly ischemic stroke, increased with elevated BMI values in another study (29). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increased throughout the range of moderate and severe excess weight for both genders in all age groups (19). The female predominance of the umbilical hernias in adults may also be explained by pregnancies and the higher prevalence of obesity in females. But hormonal status of females

and some other factors should take additional roles in the process to be able to explain the high prevalence of umbilical hernias even in the period of infancy in females. Similarly, varicous dilatations in the lower extremities are much more common in females, and most of them develop during labors, probably due to vasodilatory effects of estrogen. These vasodilatation may also disturb the abdominal wall muscles in women in the process of umbilical hernias.

Cirrhosis may actually be a systemic inflammatory process prominently affecting the hepatic vasculature. The origin of the inflammation is unclear but aging, smoking, alcohol, local and systemic inflammatory or infectious processes, and excess weight may be the major underlying causes. The inflammation is enhanced by release of various chemicals by lymphocytes to repair the damaged hepatic tissues, especially endothelial cells of hepatic arteriols (30). Due to the continuous irritation process of the endothelial cells in case of aging, smoking, alcohol, local and systemic inflammatory or infectious processes, or excess weight, prominent changes develop in the architecture of the hepatic tissue, since the chronic inflammatory process of the endothelial cells terminates with atherosclerosis, tissue hypoxia and infarcts, and fibrosis. Metabolic abnormalities such as dyslipidemia, hyperglycemia, and insulin resistance cause various cellular responses that induce tissue inflammation and immune cell activation, which in turn exacerbate the systemic atherosclerotic process (31). Although cirrhosis is mainly be an accelerated atherosclerotic process of the hepatic vasculature, there are several evidences about coexistence of a systemic endothelial inflammation all over the body. For instance, there may be close relationships between cirrhosis and CHD, COPD, PAD, CRD, and stroke-like other terminal endpoints of the metabolic syndrome, probably due to the underlying systemic atherosclerotic process (32). Similarly, most of the mortality cases in cirrhosis may actually be caused by cardiovascular diseases, and CHD may be the most common one among them (33). On the other hand, nonalcoholic fatty liver disease (NAFLD) is a term used to define a spectrum of disorders characterized by macrovesicular steatosis which occurs in the absence of consumption of alcohol in amount considered to be harmful to the liver. Since the risk of NAFLD is directly proportional to the BMI, and there is a high prevalence of excess weight in the society, NAFLD is also becoming a significant health problem all over the world. According to the literature, sustained hepatic injury will lead to progressive fibrosis and cirrhosis in up to 25% of cases with NAFLD (34). Excessive fat accumulation in hepatocytes is called as hepatosteatosis. It progresses to NAFLD, steatohepatitis, fibrosis, cirrhosis, hepatocellular carcinoma, and eventually hepatic failure. There are two histologic patterns of NAFLD including fatty liver alone and nonalcoholic steatohepatitis (NASH). NASH represents a shift from simple steatosis to an inflammatory process. Excess weight may be the major cause of exacerbation of hepatic inflammation and fibrogenesis in the NASH. NAFLD affects up to one third of the world population, and it is the most common cause of chronic liver disease even in children and adolescents in the world (35, 36). The recent increase in the prevalence of excess weight likely explains the NAFLD epidemic, worldwide (32). NAFLD is combined with a low-grade chronic inflammatory state, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (32). NAFLD shares many features of the metabolic syndrome as a highly atherogenic condition, and it may cause hepatic inflammation and cellular injury, particularly at the endothelial level. Beside terminating with cirrhosis, NAFLD is associated with a higher overall mortality and an increased prevalence of cardiovascular diseases (36). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased intima-media thickness of the carotid artery as the reliable markers of subclinical atherosclerosis (32). So NAFLD may also be a predictor of cardiovascular diseases (37). NAFLD may actually be considered as a hepatic component of the metabolic syndrome since hepatic fat accumulation is highly correlated with the components of the metabolic syndrome (38). Similar to the present study, although the prevalence of dyslipidemia was significantly lower in the normal weight than the overweight groups (25.0% versus 45.2%, $p<0.001$), there was a nonsignificant difference between the overweight and obesity groups (45.2% versus 37.5%, $p>0.05$) (39). These findings may be explained by the hepatic fat accumulation, inflammation, and fibrosis induced relatively lost hepatic functions in obesity.

WCH is a condition characterized by elevated BP in medical settings combined with normal ABP or self-measured HBP. As already detected in the literature (11, 40), the both methods are equally effective for diagnosis of the WCH. Similarly, recent HT guidelines propose self-measurement of HBP as an important technique to evaluate response to antihypertensive therapy, to improve compliance with the therapy, and as an alternative to ABP to confirm or refute WCH (41). We detected very high prevalences of WCH in the society, 33.3% in the second, 46.6% in the third, 50.0% in the fourth, 48.9% in the fifth, 36.9% in the sixth decades of life (11). Prevalence of HT initially started to be higher than 40% in the sixth decade, and it reached up to 75% in the eighth decade of life (11). On the other hand, the prevalences of HT were detected as 3% in the third, 8% in the fourth, and 21% in the fifth decades of life (11). The high prevalences of WCH in the society were also shown in some other studies, too (42, 43). Eventually, we come to the result that all HT cases, 75% in the eighth decade, may develop from the previous WCH cases, but WCH may actually be an acute phase reactant (APR) for several consequences instead of being a precursor sign of overt HT alone (11). Although the patients with WCH are characterized by absence of target organ damage induced by HT, absence of risk of cardiovascular diseases related to HT, and absence of lowering of BP with the antihypertensive therapies in a recent review (44), we evaluated WCH not just as a precursor sign

of overt HT alone but as an APR mainly alarming the excess weight and several consequences of it in the future (45). When we compared the underweight, normal weight, and overweight groups, beside decreased prevalences of sustained normotension (NT) from the underweight towards the normal weight and overweight groups, the prevalences of WCH increased in the same direction, significantly (45). Eventually, the prevalence of WCH reached up to 68.1% in the overweight group, and only 31.8% of the overweight cases have sustained NT although the relatively younger mean age of them. Similarly, although the lower prevalences of overweight and obesity in the early decades, we detected the prevalences of WCH as 33.3% even in the second and 46.6% in the third decades of life (11). On the other hand, when we compared the sustained NT, WCH, and overt HT groups (40), WCH cases were found in between according to frequencies of nearly all of the following disorders including obesity, impaired glucose tolerance, DM, hypertriglyceridemia, hyperbetalipoproteinemia, and dyslipidemia. Nearly all of the disorders showed a gradual progression in frequency from the sustained NT towards the WCH and HT groups (40). On the other hand, 20.0% and 35.5% of WCH cases in the underweight and the normal weight groups, respectively, may indicate that WCH may be an APR influenced by several factors instead of BMI alone (45).

As a conclusion, there may be significant relationships between the umbilical hernia, obesity, cirrhosis, and other terminal endpoints of the metabolic syndrome including HT, DM, and CHD in adults, probably on the bases of prolonged inflammatory, atherosclerotic, and pressure effects of excessive fat tissue on abdominal wall muscles. The inverse relationships between obesity and hypertriglyceridemia and hyperbetalipoproteinemia may be explained by the hepatic fat accumulation, inflammation, and fibrosis induced relatively lost hepatic functions in obesity. Similarly, the inverse relationship between obesity and WCH may be explained by progression of WCH into overt HT in obesity. So obesity may actually be a precirrhotic condition in adults.

References

1. Helvaci MR, Kaya H, Seyhanli M, Yalcin A. White coat hypertension in definition of metabolic syndrome. Int Heart J 2008; 49(4): 449-57.

2. Helvaci MR, Kaya H, Gundogdu M. Association of increased triglyceride levels in metabolic syndrome with coronary artery disease. Pak J Med Sci 2010; 26(3): 667-72.

3. Helvaci 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(3): 376-9.

4. Helvaci MR, Kaya H, Gundogdu M. White coat hypertension may be an initial sign of metabolic syndrome. Acta Med Indones 2012; 44(3): 222-7.

5. Helvaci MR, Aydin Y, Gundogdu M. Body mass index or body weight alone. World Family Med 2013; 11(7): 43-7.

6. Helvaci MR, Davarci M, Ozkan OV, Semerci E, Abyad A, Pocock L. Cholelithiasis may also be a consequence of metabolic syndrome. World Family Med 2017; 15(5): 9-13.

7. Helvaci MR, Ayyildiz O, Gundogdu M, Aydin Y, Abyad A, Pocock L. Hyperlipoproteinemias may actually be acute phase reactants in the plasma. World Family Med 2018; 16(1): 7-10.

8. Helvaci MR, Ayyildiz O, Gundogdu M, Aydin Y, Abyad A, Pocock L. Excess weight or smoking. World Family Med 2018; 16(10): 14-9.

9. 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; 17: 106(25): 3143-421.

10. 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(5): 821-48.

11. Helvaci MR, Seyhanli M. What a high prevalence of white coat hypertension in society! Intern Med 2006; 45(10): 671-4.

12. Mawera G, Muguti GI. Umbilical hernia in Bulawayo: some observations from a hospital based study. Cent Afr J Med 1994; 40(11): 319-23.

13. Mittelstaedt WE, Rebelatto FJ, Uchôa MC, Souza JF, Pires PW, Speranzini M, et al. Umbilical hernia ill adults. Review of 291 cases treated at the Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo. Rev Hosp Clin Fac Med Sao Paulo 1988; 43(1): 51-8.

14. Morgan WW, White JJ, Stumbaugh S, Haller JA Jr. Prophylactic umbilical hernia repair in childhood to prevent adult incarceration. Surg Clin North Am 1970; 50(4): 839-45.

15. Chu KM, McCaughan GW. Iatrogenic incarceration of umbilical hernia in cirrhotic patients with ascites. Am J Gastroenterol 1995; 90(11): 2058-9.

16. Belghiti J, Durand F. Abdominal wall hernias in the setting of cirrhosis. Semin Liver Dis 1997; 17(3): 219-26.

17. Chevrel JP. Inguinal, crural, umbilical hernias. Physiopathology, diagnosis, complications, treatment. Rev Prat 1996; 46(8): l015-23.

18. Askar OM. Aponeurotic hernias. Recent observations upon paraumbilical and epigastric hernias. Surg Clin North Am 1984; 64(2): 315-33.

19. 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(15): 1097-105.

20. Helvaci MR, Aydin Y, Gundogdu M. Smoking induced atherosclerosis in cancers. HealthMED 2012; 6(11): 3744-9.

21. De Pergola G, Pannacciulli N. Coagulation and fibrinolysis abnormalities in obesity. J Endocrinol Invest 2002; 25(10): 899-904.

22. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999; 340(2): 115-26.

23. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103(13): 1813-8.

24. Ridker PM. High-sensitivity C-reactive protein and cardiovascular risk: rationale for screening and primary prevention. Am J Cardiol 2003; 92(4B): 17-22.

25. 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(18): 1477-82.

26. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999; 282(22): 2131-5.

27. 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(2): 202-6.

28. 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(3): 147-56.

29. 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(3): 245-52.

30. Mostafa A, Mohamed MK, Saeed M, Hasan A, Fontanet A, Godsland I, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. Gut 2010; 59(8): 1135-40.

31. Xia M, Guerra N, Sukhova GK, Yang K, Miller CK, Shi GP, et al. Immune activation resulting from NKG2D/ligand interaction promotes atherosclerosis. Circulation 2011; 124(25): 2933-43.

32. Bonora E, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. Nat Rev Gastroenterol Hepatol 2012; 9(7): 372-81.

33. Anderson RN, Smith BL. Deaths: leading causes for 2001. Natl Vital Stat Rep 2003; 52(9): 1-85.

34. Sanyal AJ, American Gastroenterological Association. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002; 123(5): 1705-25.

35. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur Heart J 2012; 33(10): 1190-200.

36. Pacifico L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. World J Gastroenterol 2011; 17(26): 3082-91.

37. Mawatari S, Uto H, Tsubouchi H. Chronic liver disease and arteriosclerosis. Nihon Rinsho 2011; 69(1): 153-7.

38. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des 2010; 16(17): 1941-51.

39. Helvaci MR, Ayyildiz O, Algin MC, Aydin Y, Abyad A, Pocock L. Alanine aminotransferase indicates excess weight and dyslipidemia. World Family Med 2017; 15(9): 13-7.

40. Helvaci MR, Kaya H, Seyhanli M, Cosar E. White Coat Hypertension Is Associated with a Greater All-cause Mortality. J Health Sci 2007; 53(2): 156-60.

41. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289(19): 2560-72.

42. Hozawa A, Ohkubo T, Kikuya M, Yamaguchi J, Ohmori K, Fujiwara T, et al. Blood pressure control assessed by home, ambulatory and conventional blood pressure measurements in the Japanese general population: the Ohasama study. Hypertens Res 2002; 25(1): 57-63.

43. Celis H, Fagard RH. White-coat hypertension: a clinical review. Eur J Intern Med 2004; 15(6): 348-57.

44. Verdecchia P, Staessen JA, White WB, Imai Y, O'Brien E. Properly defining white coat hypertension. Eur Heart J 2002; 23(2): 106-9.

45. Helvaci MR, Kaya H, Yalcin A, Kuvandik G. Prevalence of white coat hypertension in underweight and overweight subjects. Int Heart J 2007; 48(5): 605-13.