Journal of Obesity and Chronic Diseases

https://doi.org/10.17756/jocd.2018-016

Review Article

Open Access

The Answer to Why Some Are Obese but Healthy?!

DV. Muralidhara

Chief Research Officer, Father Muller Medical College, Mangalore, Karnataka, India

*Correspondence to:
DV. Muralidhara
Chief Research Officer
Father Muller Medical College
Mangalore, Karnataka, India
E-mail: diviem@yahoo.com

Received: March 13, 2018
Accepted: June 15, 2018
Published: June 19, 2018

Citation: Muralidhara DV. 2018. The Answer to Why Some Are Obese but Healthy?! *J Obes Chronic Dis* 2(1): 37-43.

Copyright: © 2018 Muralidhara. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY) (http://creativecommons.org/licenses/by/4.0/) which permits commercial use, including reproduction, adaptation, and distribution of the article provided the original author and source are credited.

Published by United Scientific Group

Abstract

Obesity is a complex issue involving both physical and metabolic dysfunction. Some obese individuals are spared from the unfavorable metabolic disturbances often seen in that condition. Such individuals are referred to as healthy obese persons who constitute a considerable proportion of the obese group of subjects. The possible roles of several important adipokines that are studied in this regard are presented in this communication. The importance of such group of obese individuals and other variant such as metabolically obese with normal body weight status and other challenges faced is pointed out both for clinical and research purposes.

Keywords

Obesity, Healthy obesity, Metabolic disturbances, Adipokines, Inflammation

Obesity and Favorable Metabolic Profile

Human obesity has been documented long back [1]. WAT has a role in the regulation of whole-body energy metabolism and its endocrine function has a critical role in the development of obesity and its metabolic and cardiovascular complications by secreting cytokines/adipokines in distorted proportions. In obese individuals, monocyte and B and T lymphocyte infiltration into the adipose tissue results in low-grade inflammatory state associated with a rise in circulating C-reactive protein (CRP) which could be used as a marker for the development of type 2 diabetes mellitus (T2DM) and insulin resistance (IR) [2-4]. However, it should be noted that obesity itself will not lead to the development of IR but, the adipose tissue inflammatory condition is the culprit in metabolic disorders of humans [2]. This fact is further supported by a study on metabolically normal obese postmenopausal women who had exhibited lower CRP and alpha-1 antitrypsin levels suggesting a protective role of these inflammatory markers against cardiometabolic risks [5].

Recent advances in obesity research deny some of the generalizations made commonly on excess body weight and health. For example, just the extra body fat does not always result in higher health risks or the lower body fat levels provide risk free health status is a very appropriate one to consider [6]. Interestingly, some obese persons with elevated body fat mass are free from cardiovascular and metabolic risks. They exhibit a healthy inflammatory status, good lipid profile and less insulin resistance with no signs of hypertension. Such individuals are at a lower risk as compared to metabolically unhealthy obese (MUHO) individuals and hence called metabolically healthy obese (MHO) persons [7, 8]. The black obese people and the Japanese sumo wrestlers who have very little visceral fat and heavy muscle mass have a greater tendency of being metabolically healthy when compared with their respective control subjects [9, 10]. Another study by

Meigs et al., involving nearly 3000 men and women has shown that the MHO subjects were at no higher risk of developing cardiovascular disease or T2DM, when compared to healthy normal weight individuals [11]. In one more work, Albrink and Meigs [12] have reported that many of their obese subjects had healthy levels of triglycerides. A study on liver enzymes in MHO postmenopausal women has shown healthy levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) [13]. Reduced amounts of liver enzymes, especially lower circulating ALT may represent lower hepatic insulin resistance and reduced liver fat content that may be partly responsible for the favorable metabolic profile of MHO individuals. Evidence also from animal studies in which healthy obese mice lacked a protein called collagen VI was metabolically much better without developing inflammation or IR than their counterpart that had the collagen VI also supports the view on MHO [14].

Available studies report that 20-30% of such obese individuals appear to be in metabolically healthy category [9, 11, 15, 16]. These individuals have been differently referred to as 'metabolically normal obese' (MNO), 'metabolically healthy but obese' (MHO), 'obese but metabolically normal' (OMN) or as having metabolically uncomplicated obesity or 'Healthy Obese' subtype [17]. However, there is no consistent method to define MHO individuals [18]. Though, some suggestions have been made [9, 19, 20], it should be noted that the criteria could be modified and that the cut-off points should be refined particularly for blood pressure, waist circumference, fasting glucose and eventually post-load glycemia. On the other hand, lean individuals can also develop acute inflammation-induced insulin resistance, even without having extra body fat. This subgroup is referred to as metabolically obese but normal weight (MONW) type [9]. A recent study has reported that a lean insulin-resistant subject may have elevated pro-inflammatory markers such as MCP-1, IL-6 and resistin than an overweight, insulin sensitive subject [21]. The characteristics of these different groups are shown in table 1.

Table 1: Clinical and diagnostic characteristics of the sub-types of obesity as compared to a normal healthy individual [71].

Variables	Metabolically healthy & normal weight (MHNW)	Metabolically unhealthy Obese (MUHO)	Metabolically healthy obese (MHO)	Metabolically obese normal weight (MONW)
BMI	↓	↑	↑	↓
Total fat mass	↓	↑	↑	↑
Visceral fat	↓	↑	↓	↑
Liver fat	↓	↑	↓	↑
Muscle fat	↓	↑	↓	↑
Triglycerides	↓	↑	↓	↑
HDL Cholesterol	↑	↓	↑	↓
Lean body mass	↑	↓	↑	↓
Insulin resistance	↓	↑	↓	↑
Insulin secretion	Normal	↑	Normal	↑
Onset of obesity	---	Late onset	Early onset	Late onset

Prevalence

MHO individuals represent a very challenging subgroup. Wildman and his colleagues in their study have reported that 51.3% of overweight and 31.7% of obese adults were MHO [9]. Others have reported a prevalence from 6% to 40% in different overweight and obese populations [11, 20, 22, 23]. Data available from a limited number of studies from the West shows the prevalence of MHO ranging from 11-40% whereas the prevalence of MONW is about 5-45% [24]. A recent study from Korea involving over 5000 subjects [25] also asserts this view and it reports that 48% of the lesser age and about 13% of the older age group is MHO. The major cause of such a wide difference may be due to differences in study design and how the metabolic health is defined. However, no such data is available as yet for Asian countries.

What Contributes to MHO?

What contributes to this phenomenon of MHO is not clear but a significant role for adipokines has been suggested. However, some reports on the possible role of leptin, adiponectin, and resistin in MHO have indicated that higher leptin levels, leptin/adiponectin ratio, and lower adiponectin contribute to the increased risk of hypertension in MHO both in children and adolescents and elevated adiponectin level among obese women could be presumably provide a favorable metabolic profile [26, 27]. A few studies have shown that circulating adipokines such as chemerin and retinol-binding protein-4 were significantly low in MHO subjects as compared to metabolically unhealthy obese (MUO) individuals [28]. So also, in MHO individuals circulating levels of total adiponectin or high molecular weight adiponectin [28, 29] similar to lean healthy (LH) individuals and increased levels as compared MUO individuals have been reported. Phillips et al. [30] have recently shown that MHO and LH individuals have significantly lower concentrations of plasminogen activator inhibitor-1, as well as higher adiponectin levels, compared with their MUO counterpart. It was also found that MHO individuals had lower blood levels of fetuin-A, (a hepatokine) that was associated with improved insulin sensitivity and glucose homeostasis as compared with MUO individuals [28, 31].

Therefore, understanding the interplay of adipokines is vital that might explain why some obese individuals develop complications, and others do not. Adipose tissue, now established as the largest endocrine organ secretes various bioactive molecules called adipokines that have many different biological effects [32]. It secretes leptin, adiponectin, resistin, interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) and monocyte chemotactic protein-1 (MCP-1) and

many other cytokines. Adipokines are grouped into hormones, growth factors, angiogenic factors, and cytokines. Of all the adipokines, leptin, adiponectin, resistin, monocytes, and macrophage chemotactic protein 1 (chemokine [C-C motif] ligand [CCL]-2), interleukin (IL)-6, IL-1β, tumor-necrosis factor (TNF), anti-inflammatory IL-10, and transforming growth factor (TGF)-β are often studied ones [33]. A summary of the functions of these adipokines in health and changes in their levels in obesity is given in table 2.

foam cells in the vessel wall providing the anti-inflammatory and antiatherogenic effects. Additionally, adiponectin also increases insulin sensitivity, fatty acid oxidation and decreases secretion of glucose from liver, increases glucose uptake, and adipogenesis [22, 33, 36]. Adiponectin also promotes glucose metabolism and accelerates the oxidation of free fatty acids in the muscle [37, 38]. In total these are favorable effects of adinopectin to prevent the negative metabolic and cardiovascular effects in obesity.

Table 2: Important adipokines and their functions.

Adipokine	Major functions		Changes in obese individuals
	Increase	Decrease	
Leptin	Energy expenditure.	Food-intake.	Increased adipocytes expression/secretion, leptin resistance, hyperleptinemia, Inflammatory cell activation.
Adiponectin	Insulin sensitivity, fatty acid oxidation, adipose tissue glucose uptake, adipogenesis, glucose metabolism.	Free fatty acid uptake, glucose secretion in the liver, anti-inflammatory, antiatherogenic, and antidiabetic actions.	Decreased expression and secretion in adipose tissue and serum levels.
Resistin	Insulin resistance, proinflammatory cytokines secretion, adhesion molecules.		Increased serum levels in mice. Controversial results in humans.
TNF	Inflammation, lipolysis in adipose tissue.	Insulin signaling.	Increased expression and secretion in adipose tissue.
iL-6	Insulin signaling, release of free fatty acids (adipose tissue).	Metabolic actions.	Increased expression and secretion in adipose tissue and serum levels.
CCL2	Macrophage infiltration and adipose tissue inflammation.		Increased serum levels and expression in adipose tissue.
iL-10		Macrophage activity, proinflammatory cytokine synthesis.	Increased serum levels but, decreased in metabolic syndrome (in women).
TGFβ		Growth and activation of immune cells, macrophage activation, T- and B-cell activation.	Increased both in humans and animals.

Note: TNF: tumor-necrosis factor; **iL:** interleukin; **CCL:** chemokine (C-C motif) ligand; **TGF:** transforming growth factor

Role of Some Important Adipokines

Leptin

Leptin is mainly secreted by subcutaneous adipose tissue. It plays an important role in the regulation of food intake and also promotes energy expenditure. It affects heat production, lipid metabolism, blood cells production, activity of the ovary and β-cell function [33, 34]. Obesity is closely related to leptin resistance leading to increased blood levels of leptin [35]. Leptin controls the expression of pro-inflammatory cytokines in macrophages and T cells and induces inflammation. Interactions between leptin and inflammation play a vital role in maintaining chronic inflammatory state in obesity which leads to more and more secretion of leptin [33].

Adiponectin

Like leptin, adiponectin is primarily secreted in subcutaneous adipose tissue. Adiponectin has antidiabetic, anti-inflammatory, antiatherogenic (pro-angiogenic) and anti-apoptotic effects. It also limits the infiltration of monocytes/macrophages into adipose tissue and their conversion into

There is an inverse relationship between circulating adiponectin level and body mass index (BMI), waist circumference, body fat percentage and insulin resistance. Adinopectin concentration is reduced in diabetes, hypertension and coronary arterial disease. Such an observation of low adinopectin levels is made among the Pima Indians, who have high prevalence of 2TDM, while subjects with high adiponectin levels were found to be less likely to develop diabetes than those with low concentrations. This finding indicates the protective effect of adinopectin in such individuals with greater tendency of developing diabetes [39]. Similar studies on obese African Americans with hyperadiponectinemia also had shown a healthier metabolic profile, including increased high-density lipid cholesterol, lower insulin levels, smaller waist circumference, lower insulin levels and favorable inflammatory profile as compared to those without hyperadiponectinemia [29, 40].

Although it has been shown previously that serum leptin correlates positively with BMI and body fat %, its level in the MHO group was similar to that of the metabolically unhealthy group [41]. Adiponectin and leptin are closely involved in fat

metabolism and act as important mediators of atherosclerosis in obesity. Therefore, when leptin to adiponectin ratio was considered, it was less in the MHO subjects as compared to the metabolically unhealthy group. This ratio could therefore, be an indirect marker to evaluate metabolic syndrome and atherosclerosis in obese T2DM patients [42, 43].

Resistin

Resistin is a pro-inflammatory cytokine. It interferes with the action of insulin resulting in IR [44, 45]. Data on human resistin studies are less uniform. However, in metabolically healthy subjects resistin levels are low as compared to metabolic syndrome patients [29]. Resistin has a role in atherosclerosis in humans. It acts on endothelial cells by promoting the expression of endothelin-1, the intercellular adhesion molecule and the vascular cell-adhesion molecule [46]. It also contributes to a number of disease conditions such as autoimmune diseases, nonalcoholic fatty liver disease, malignancies, asthma, inflammatory bowel disease and chronic kidney disease [44].

Tumor-necrosis factor (TNF)

TNF-α in obese individual is produced by M1 macrophage from the stromal vascular fraction of adipose tissue [37, 47, 48]. TNF is high in obesity and has a role in the pathogenesis of IR [49] and metabolic syndrome [50]. TNF is also indicated in interlekin-6 (IL-6) and chemokine ligand 2 (CCL2) secretion that have proinflammatory actions. Lean insulin-resistant individuals will have increased levels of inflammatory biomarkers as compared to an overweight person with no insulin resistance. Interestingly, MHO individuals have lower levels of TNF and a decreased pro-inflammatory profile.

Interleukin-6 (IL-6)

IL-6 is secreted by several different tissues and has multiple roles. It regulates insulin signaling and lipid metabolism in peripheral tissues along with its inflammation and host defense role [51]. Obesity, glucose intolerance and insulin resistance is positively correlated with increased IL-6 and can predict the development of T2DM, metabolic syndrome, and cardiovascular disease [47]. Weight loss reduces blood levels of IL-6 and also its expression by adipose tissue. Comparable IL-6 and CRP serum levels have been reported in lean and MHO subjects, but were less than the unhealthy obese [52, 53].

Chemokine ligand 2 (CCL2)

In humans, CCL2 or monocyte chemotactic protein-1 (MCP-1) secreted mainly by macrophages and endothelial cells, increases the secretions of pro-inflammatory cytokines by recruiting monocytes to the inflammatory site. Insulin-resistant obese subjects will have raised plasma levels of CCL2 and adipose-tissue over-expression. In contrast, MHO individuals display a reduced inflammatory profile contributed by less number of infiltrating adipose tissue macrophages and crown-like structures in adipose tissue and also by reduced serum levels of CCL2 [54].

Interleukin-10 (IL-10)

IL-10 provides an anti-inflammatory environment in adipose tissue under physiological conditions [55]. However, IL-10 profile in the MHO is so far unknown. But, it is possible to suggest that its levels are positively correlated in subjects with MHO phenotype because of its anti-inflammatory properties.

Other adipokines

Chemerin has important roles in inflammation, metabolism and acts as a link between chronic inflammation, obesity and obesity associated co-morbidities. Interestingly, chemerin has been assigned both a proinflammatory and anti-inflammatory actions [56, 57].

Orosomucoid modulates the immune responses from excessive inflammation and metabolic disturbances and thus has a protective role on adipose tissue [52, 57, 58]. Its secretion from the adipocytes markedly increases in inflammatory and metabolic stress conditions and also by TNF-α, insulin, glucose and free fatty acids [59]. It is believed that there is a positive correlation between circulating orosomucoid levels and BMI and body fat mass rather than the metabolic status of the individual [58].

Two other adipokines namely, omentin and vaspin have anti-inflammatory effects that will result in improving IR while lipocalin 2 and visfatin are pro-inflammatory adipokines that promotes TNF expression in the adipose tissue [60]. More recently, it has been shown that plasminogen activator inhibitor-1 (PAI-1) levels are high in obese subjects, which has been further substantiated by several interventional studies where PAI-1 levels reduced significantly after obese people lost weight [61].

Challenges

The following challenges are to be addressed regarding obesity.

A) A proper clinical classification of health risk in obesity,

B) Identification and treatment prioritization of obese individuals at highest risk of developing disease and early mortality [18]. Furthermore, it is now believed that all the MHO individuals may not be in good health and it is not certain for how long they maintain good health status during their entire life time! Appleton et al., reported that the MHO phenotype was stable for 67% of their study participants over a 10-year period [62], suggesting that MHO individuals may have greater resistance to the development of obesity-related complications and in contrast, another study has suggested that excess body weight compromises long-term health [63].

Several other studies have suggested an increased risk for long-term adverse effects including cardiometabolic complications even in the absence of metabolic abnormalities in obese persons [64]. Dobson et al. [65] have hypothesized that metabolically unhealthy individuals irrespective of their BMI, would have adverse levels of ectopic fat (visceral and liver fat deposition) and myocardial dysfunction compared with MHO individuals. Morkedal et al. [66] have revealed that there is no relationship between acute myocardial infarction and MHO

subjects, but, have established an association with increased risk for heart failure in MHO subjects particularly for long-lasting or severe obesity. Furthermore, excess accumulation of ectopic fat in liver, skeletal muscle, and pancreas is known to contribute to metabolic disturbances [67]. For example, Ogorodnikova and his co-workers have reported that MHO women had intermediate levels of epicardial, pericardial and hepatic fat as compared to lean healthy and MUO women and were associated with insulin resistance [68].

Another question to answer is, should such MHO individuals lose body weight? However, different opinions have been put forth in this regard [6, 69, 70]. Otherwise, to treat all obese patients with the idea of 'one size fits all' may be counterproductive.

Conclusion

The pathogenesis of metabolic disorders associated with obesity is closely related to adipokine secretion pattern from adipose tissue. Adipokines are important biomolecules that play a major part in inflammation and IR in obesity. MHO individuals being free from obesity related co-morbidities have become the target of further research. The mechanisms of favorable metabolic profile in MHO individuals thoroughly investigated can be very helpful to understand the protective factors that lead to metabolic imbalance and co-morbidities in obesity.

Of all the adipokines, it is important to note that adiponectin is a feasible and lucrative therapeutic target as it has anti-inflammatory and vascular protective effects. Several major pharmacological approaches such as (i) agents that increase the circulating concentrations of adiponectin, (ii) agents that increase adiponectin receptor expression, and (iii) agonists of the adiponectin receptor which induce signaling pathways of adiponectin receptors are currently being employed for its evaluation [71]. However, adipokine research is quite recent and is progressing in the right direction. It would take another 1-2 decade to come out with possible conclusive reports from such reports as per the expert's opinion in the field. Sometimes the inflow of information from such research is also complex and confusing that one should be extra careful and wise in accepting the findings. But, science keeps growing and one day someone will hit the target, hopefully.

In conclusion, it has been suggested that obesity for some individuals is not a serious health risk factor and might even be an advantage. Several studies on obesity have concluded that, a) there are some groups of individuals who are genetically programmed to carry extra fat and they can be considered healthy as long as they can maintain good cardiovascular health, b) there are mild or moderate benefits of obesity which is poorly understood or entirely unknown and therefore one needs to be very cautious in their weight loss programs [72]. Finally, it can be stated that the subgroups of obesity can make things interesting in three important areas; i) impact of losing weight by these individuals, ii) inclusion of these groups in obesity research and its impact on the outcome of statistical analysis and iii) including them in medical education and clinical evaluation to address the need for better characterization of such patients [72].

References

1. Francis A. 1849. Hippocrates: the genuine works of Hippocrates; translated from the Greek with a preliminary discourse and annotations. Sydenham Society, London, UK, pp 416-500.
2. Hamada M, Abe M, Miyake T, Kawasaki K, Tada F, et al. 2011. B cell-activating factor controls the production of adipokines and induces insulin resistance. *Obesity (Silver Spring)* 19(10): 1915-1922. https://doi.org/10.1038/oby.2011.165
3. Onat A, Can G, Hergenc G. 2008. Serum C-reactive protein is an independent risk factor predicting cardiometabolic risk. *Metabolism* 57(2): 207-214. https://doi.org/10.1016/j.metabol.2007.09.002
4. Jung UJ, Choi MS. 2014. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int J Mol Sci* 15(4): 6184-6223. https://doi.org/10.3390/ijms15046184
5. Karelis AD, Faraj M, Bastard JP, St-Pierre DH, Brochu M, et al. 2005. The metabolically healthy but obese individual presents a favourable inflammation profile. *J Clin Endocrinol Metab* 90(7): 4145-4150. https://doi.org/10.1210/jc.2005-0482
6. Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET. 2004. Metabolic and body composition factors in sub groups of obesity: what do we know? *J Clin Endocrinol Metab* 89(6): 2569-2575.
7. Bluher M. 2010. The distinction of metabolically 'healthy' from 'unhealthy' obese individuals. *Curr Opin Lipidol* 21(1): 38-43. https://doi.org/10.1097/MOL.0b013e3283346ccc
8. Samocha-Bonet D, Chisholm DJ, Tonks K, Campbell LV, Greenfield JR. 2012. Insulin-sensitive obesity in humans - a 'favorable fat' phenotype? *Trends Endocrinol Metab* 23(3): 116-124. https://doi.org/10.1016/j.tem.2011.12.005
9. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, et al. 2008. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med* 168(15): 1617-1624. https://doi.org/10.1001/archinte.168.15.1617
10. Matsuzawa Y. 1997. Pathophysiology and molecular mechanisms of visceral adipose fat syndrome: the Japanese experience. *Diabetes Metab Rev* 13(1): 3-13.
11. Meigs JB, Wilson PW, Fox CS, Vasan RS, Nathan DM, et al. 2006. Body mass index, metabolic syndrome and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab* 91(8): 2906-2912. https://doi.org/10.1210/jc.2006-0594
12. Albrink MJ, Meigs JW. 1965. The relationship between serum triglycerides and skin fold thickness in obese subjects. *Ann NY Acad Sci* 131(1): 673-683.
13. Messier V, Karelis AD, Robillard ME, Bellefeuille P, Brochu M, et al. 2010. Metabolically healthy but obese individuals: relationship with hepatic enzymes. *Metabolism* 59(1): 20-24. https://doi.org/10.1016/j.metabol.2009.06.020
14. Khan T, Muise ES, Iyengar P, Wang ZV, Chandalia M, et al. 2009. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI. *Mol Cell Biol* 29(6): 1575-1591. https://doi.org/10.1128/MCB.01300-08
15. Karelis AD, Brochu M, Rabasa-Lhoret R. 2004. Can we identify metabolically healthy but obese individuals (MHO)? *Diabetes Metab* 30(6): 569-572.
16. Iacobelllis G, Ribaudo MC, Zappaterreno A, Ianunucci CV, Leonetti F. 2005. Prevalence of uncomplicated obesity in an Italian obese population. *Obesity Res* 13(6): 1116-1122. https://doi.org/10.1038/oby.2005.130

17. Hayes L, Pearce MS, Firbank M, Walker M, Taylor R, et al. 2010. Do obese but metabolically normal women differ in intra-abdominal fat and physical activity levels from those with the expected metabolic abnormalities? A cross sectional study. *BMC Public Health* 10: 723 https://doi.org/10.1186/1471-2458-10-723
18. Karelis AD. 2008. Metabolically healthy but obese individuals. *Lancet* 372(9642): 1281-1283. https://doi.org/10.1016/S0140-6736(08)61531-7
19. Brochu M, Tchernof A, Dionne IJ, Sites CK, Eltabbakh GH, et al. 2001. What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? *J Clin Endocrinol Metab* 86(3): 1020-1025. https://doi.org/10.1210/jcem.86.3.7365
20. Stephan N, Kantartzis K, Machann J, Schick F, Thamer C, et al. 2008. Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med* 168(15): 1609-1616. https://doi.org/10.1001/archinte.168.15.1609
21. Moscavitch SD, Kang HC, Filho RA, Mesquita ET, Neto HC, et al. 2016. Comparison of adipokines in a cross-sectional study overweight, insulin-sensitive and healthy lean, with healthy insulin-resistant subjects, assisted by a family doctor primary care program. *Diabetol Metab Syndr* 8:9. https://doi.org/10.1186/s13098-016-0125-9
22. Aguilar-Salinas CA, García EG, Robles L, Riaño D, Ruiz-Gomez DG, et al. 2008. High adiponectin concentrations are associated with the metabolically healthy obese phenotype. *J Clin Endocrinol Metab* 93(10): 4075-4079. https://doi.org/10.1210/jc.2007-2724
23. Phillips CM. 2013. Metabolically healthy obesity: definitions, determinants and clinical implications. *Rev Endocr Metabol Disor* 14(3): 219-27. https://doi.org/10.1007/s11154-013-9252-x
24. Conus F, Rabasa-Lhoret R, Peronnet F. 2007. Characteristics of metabolically obese normal weight (MONW) subjects. *Appl Physiol Nutr Metab* 32(1): 4-12. https://doi.org/10.1139/H07-926
25. Lee K. 2009. Metabolically obese but normal weight (MONW) and metabolically healthy but obese (MHO) phenotypes in Koreans: characteristics and health behaviors. *Asia Pac J Clin Nutr* 18(2): 280-284.
26. Ding W, Cheng H, Chen F, Yan Y, Zhang M, et al. 2018. Adipokines are associated with hypertension in metabolically healthy obese (MHO) children and adolescents: a prospective population-based cohort study. *J Epidemiol* 28(1): 19-26. https://doi.org/10.2188/jea.JE20160141
27. Boyarinova MA, Orlov AV, Rotar OP, Alieva AS, Moguchaya EV, et al. 2016. Adipokines level in metabolically healthy obese saint-petersburg inhabitants (ESSE-RF). *Kardiologiia* 56(8): 40-45. https://doi.org/10.18565/cardio.2016.8.40-45
28. Kloting N, Fasshauer M, Dietrich A, Kovacs P, Schon MR, et al. 2010. Insulin-sensitive obesity. *Am J Physiol Endocrinol Metab* 299(3): E506–E515. https://doi.org/10.1152/ajpendo.00586.2009
29. Doumatey AP, Bentley AR, Zhou J, Huang H, Adeyemo A, et al. 2012. Paradoxical hyperadiponectinemia is associated with the metabolically healthy obese (MHO) phenotype in African Americans. *J Endocrinol Metab* 2(2): 51-65. https://doi.org/10.4021/jem95W
30. Phillips CM, Perry IJ. 2013. Does inflammation determine metabolic health status in obese and non-obese adults? *J Clin Endocrinol Metab* 98(10): E1610–E1619. https://doi.org/10.1210/jc.2013-2038
31. Stefan N, Fritsche A, Weikert C, Boeing H, Joost HG, et al. 2008. Plasma fetuin-A levels and the risk of type 2 diabetes. *Diabetes* 57(10): 2762-2767. https://doi.org/10.2337/db08-0538
32. Muralidhara DV. 2016. Understanding the physiology of adipose tissue: a key to combat obesity? *J Obes Management* 1(2): 1-15. https://doi.org/10.14302/issn.2574-450X.jom-16-1268
33. Leal VO, Mafra D. 2013. Adipokines in obesity. *Clin Chim Acta* 419: 87-94. https://doi.org/10.1016/j.cca.2013.02.003
34. Becer E, Mehmetçik G, Bareke H, Serakıncı N. 2013. Association of leptin receptor gene Q223R polymorphism on lipid profiles in comparison study between obese and non-obese subjects. *Gene* 529(1): 16-20. https://doi.org/10.1016/j.gene.2013.08.003
35. Jung CH, Kim MS. 2013. Molecular mechanisms of central leptin resistance in obesity. *Arch Pharm Res* 36(2): 201-207. https://doi.org/10.1007/s12272-013-0020-y
36. Fu Y, Luo N, Klein RL, Garvey WT. 2005. Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation. *J Lipid Res* 46(7): 1369-1379. https://doi.org/10.1194/jlr.M400373-JLR200
37. Coelho M, Oliveira T, Fernandes R. 2013. Biochemistry of adipose tissue: an endocrine organ. *Arch Med Sci* 9(2): 191-200. https://doi.org/10.5114/aoms.2013.33181
38. Lenz A, Diamond FB Jr. 2008. Obesity: the hormonal milieu. *Curr Opin Endocrinol Diabetes Obes* 15(1): 9-20. https://doi.org/10.1097/MED.0b013e3282f43a5b
39. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, et al. 2002. Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 360(9326): 57–58. https://doi.org/10.1016/S0140-6736(02)09335-2
40. Bik W, Ostrowski J, Baranowska-Bik A, Wolinska-Witort E, Bialkowska M, et al. 2010. Adipokines and genetic factors in overweight or obese but metabolically healthy Polish women. *Neuro Endocrinol Lett* 31(4): 497-506.
41. Koster A, Stenholm S, Alley DE, Kim LJ, Simonsick EM, et al. 2010. Body fat distribution and inflammation among obese older adults with and without metabolic syndrome. *Obesity (Silver Spring)* 18(12): 2354-2361. https://doi.org/10.1038/oby.2010.86
42. Kotani K, Sakane N, Saiga K, Kurozawa Y. 2005. Leptin: adiponectin ratio as an atherosclerotic index in patients with type 2 diabetes: relationship of the index to carotid intima-media thickness. *Diabetologia* 48(12): 2684-2686.
43. Alfadda AA. 2014. Circulating adipokines in healthy versus unhealthy overweight and obese subjects. *International Journal of Endocrinology* 170434. http://doi.org/10.1155/2014/170434
44. Jamaluddin MS, Weakley SM, Yao Q, Chen C. 2012. Resistin: functional roles and therapeutic considerations for cardiovascular disease. *Br J Pharmacol* 165(3): 622-632. https://doi.org/10.1111/j.1476-5381.2011.01369.x
45. Heilbronn LK, Rood J, Janderova L, Albu JB, Kelley DE, et al. 2004. Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. *J Clin Endocrinol Metab* 89(4): 1844-1848. https://doi.org/10.1210/jc.2003-031410
46. Tsiotra PC, Boutati E, Dimitriadis G, Raptis SA. 2013. High insulin and leptin increase resistin and inflammatory cytokine production from human mononuclear cells. *Biomed Res Int* 487081. https://doi.org/10.1155/2013/487081
47. Maury E, Brichard SM. 2010. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Mol Cell Endocrinol* 314(1): 1-16. https://doi.org/10.1016/j.mce.2009.07.031
48. Galic S, Oakhill JS, Steinberg GR. 2010. Adipose tissue as an endocrine organ. *Mol Cell Endocrinol* 316(2): 129-139. https://doi.org/10.1016/j.mce.2009.08.018
49. Hotamisligil GS, Shargill NS, Spiegelman BM. 1993. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 259(5091): 87-91. https://doi.org/10.1126/science.7678183
50. Tsuriya D, Morita H, Morioka T, Takahashi N, Ito T, et al. 2011. Significant correlation between visceral adiposity and high-sensitivity C-reactive protein (hs-CRP) in Japanese subjects. *Intern Med* 50(22): 2767-2773. https://doi.org/10.2169/internalmedicine.50.5908
51. Mitrou P, Boutati E, Lambadiari V, Tsegka A, Raptis AE, et al. 2010. Insulin resistance in hyperthyroidism: the role of IL6 and TNF alpha. *Eur J Endocrinol* 162(1): 121-126. https://doi.org/10.1530/EJE-09-0622

52. Ouchi N, Parker JL, Lugus JJ, Walsh K. 2011. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 11(2): 85-97. https://doi.org/10.1038/nri2921

53. Hermsdorff HH, Zulet MA, Bressan J, Martínez JA. 2008. Effect of diet on the low-grade and chronic inflammation associated with obesity and metabolic syndrome. *Endocrinol Nutr* 55(9): 409-419. https://doi.org/10.1016/S1575-0922(08)75078-2

54. Rull A, Camps J, Alonso-Villaverde C, Joven J. 2010. Insulin resistance, inflammation, and obesity: role of monocyte chemoattractant protein-1 (or CCL2) in the regulation of metabolism. *Mediators Inflamm* 326580. https://doi.org/10.1155/2010/326580

55. Balistreri CR, Caruso C, Candore G. 2010. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators Inflamm* 802078. https://doi.org/10.1155/2010/802078

56. Rourke JL, Dranse HJ, Sinal CJ. 2013. Towards an integrative approach to understanding the role of chemerin in human health and disease. *Obesity Rev* 14(3): 245-262. https://doi.org/10.1111/obr.12009

57. Alfadda AA, Sallam RM, Chishti MA, Moustafa AS, Fatma S, et al. 2012. Differential patterns of serum concentration and adipose tissue expression of chemerin in obesity: adipose depot specificity and gender dimorphism. *Mol Cells* 33(6): 591-596. https://doi.org/10.1007/s10059-012-0012-7

58. Alfadda AA, Fatma S, Chishti MA, Al-Naami MY, Elawad R, et al. 2012. Orosomucoid serum concentrations and fat depot-specific mRNA and protein expression in humans. *Mol Cells* 33(1): 35-41. https://doi.org/10.1007/s10059-012-2181-9

59. Lee YS, Choi JW, Hwang I, Lee JW, Lee JH, et al. 2010. Adipocytokine orosomucoid integrates inflammatory and metabolic signals to preserve energy homeostasis by resolving immoderate inflammation. *J Biol Chem* 285(29): 22174-22185. https://doi.org/10.1074/jbc.M109.085464

60. Kwon H, Pessin JE. 2013. Adipokines mediate inflammation and insulin resistance. *Front Endocrinol (Lausanne)* 4:71. https://doi.org/10.3389/fendo.2013.00071

61. Folsom AR, Qamhieh HT, Wing RR, Jeffery RW, Stinson VL, et al. 1993. Impact of weight loss on plasminogen activator inhibitor (PAI-1), factor VII, and other hemostatic factors in moderately overweight adults. *Arterioscler Thromb* 13(2): 162-169.

62. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, et al. 2013. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. *Diabetes Care* 36(8): 2388-2394. https://doi.org/10.2337/dc12-1971

63. Arnlov J, Ingelsson E, Sundstrom J, Lind L. 2010. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation* 121(2): 230-236. https://doi.org/10.1161/CIRCULATIONAHA.109.887521

64. Kramer CK, Zinman B, Retnakaran R. 2013. Are metabolically healthy overweight and obesity benign conditions?: a systematic review and meta-analysis. *Ann Intern Med* 159(11): 758-769. https://doi.org/10.7326/0003-4819-159-11-201312030-00008

65. Dobson R, Burgess MI, Sprung VS, Irwin A, Hamer M, et al. 2016. Metabolically healthy and unhealthy obesity: differential effects on myocardial function according to metabolic syndrome, rather than obesity. *Int J Obes (Lond)* 40(1): 153-161. https://doi.org/10.1038/ijo.2015.151

66. Morkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. 2014. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals. HUNT (Nord-Trondelag Health Study), Norway. *J Am Coll Cardiol* 63(11): 1071-1078. https://doi.org/10.1016/j.jacc.2013.11.035

67. Thomas EL, Frost G, Taylor-Robinson SD, Bell JD. 2012. Excess body fat in obese and normal-weight subjects. *Nut Res Rev* 25(1): 150-161. https://doi.org/10.1017/S0954422412000054

68. Ogorodnikova AD, Khan UI, McGinn AP, Zeb I, Budoff MJ, et al. 2013. Ectopic fat and adipokines in metabolically benign overweight/obese women: the Kronos Early Estrogen Prevention Study. *Obesity (Silver Spring)* 21(8): 1726-1733. https://doi.org/10.1002/oby.20200

69. Sharma AM, Kushner RF. 2009. A proposed clinical staging system for obesity. *Int J Obes (Lond)* 33(3): 289-95. https://doi.org/10.1038/ijo.2009.2

70. Muralidhara DV, Mahadeva Rao US, Swethadri GK. 2012. An update on the variants of obesity. *J Pharmacol Biomed Sci* 16(16): 1-5.

71. Ziemke F, Mantzoros CS. 2010. Adiponectin in insulin resistance: lessons from translational research. *Am J Clin Nutr* 91(1): 258S-261S. https://doi.org/10.3945/ajcn.2009.28449C

72. Sims EA. 2001. Are there persons who are obese, but metabolically healthy? *Metabolism* 50(12): 1499-1504. https://doi.org/10.1053/meta.2001.27213