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Review Article

THE ASSOCIATION OF OBESITY WITH TYPE 2 DIABETES; A REVIEW

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ABSTRACT

The incidence of obesity and diabetes is recognized as a rising global epidemic. Type 2 diabetes mellitus is a significant comorbidity of obesity. Therefore often, the term 'diabesity' has been coined to describe 'obesity dependent diabetes.' The purpose of this review is to summarizes a) significant pathological factors linking obesity to diabetes, b) focusing on the current epidemiological data related to obesity and diabetes population, c) genetic determinants between them, and lastly, d) etiology and efforts to battle obesity-linked diabetes.

Keywords: diabetes, insulin resistance, obesity, etiology.

INTRODUCTION

Currently, obesity is accepted as a global epidemic (1). American medical association and world obesity federation have declared obesity as a chronic progressive disease, distinct from being just a risk factor for other diseases(2). Significant Comorbidities associated with obesity are decreased life expectancy of an estimated 5-20 years depending on severity(3, 4), metabolic diseases (type 2 DM, fatty liver disease), cardiovascular disease(hypertension, MI, stroke)(5), musculoskeletal disease(osteoarthritis), sleep apnea(6), depression, Alzheimer disease, several types of cancer(colon, rectum, prostate, endometrium, breast, kidney, liver, ovarian), endocrine changes including irregular menses, amenorrhea, and infertility in overweight women(7). Above all, It is one of the primary causes of the rising prevalence of type 2 DM(8). The association is so strong that overweight persons have a threefold risk of developing these comorbidities compared with healthy weight individuals, and obese persons are 20 times more likely to develop diabetes(6). Till now, many studies have been done to see the influence of obesity on inducing type 2 DM (9-12). Many studies also described other risk factors like physical inactivity(13), low birth weight(14), food habits, gender, age, and race that contribute to the development of type 2 D(15). we undertook a search of medical literature for articles published in the English language between 1980 and 2020. The primary purpose of this review is to estimate the influence of obesity on inducing type 2 DM. We shall also explore their current epidemiological conditions, genetically based associations, and ongoing efforts to combat obesity-linked diabetes.

1. Obesity and type 2 DM:

WHO defines obesity as an excessive accumulation of fat that might impair health and is diagnosed at a BMI of ≥30 kg/m2(16). It is a complex multifactorial disease resulting from the interaction of genetic and environmental factors. BMI is the most commonly used measurement for body adiposity(16). Among obese individuals, health risk increases with increasing BMI(17). However, BMI may not be an accurate measurement of body fat when considering specific population, due to a difference in body proportion(18). Hence anthropometric measurements like waist circumference (WC) and waist/hip ratio (WHR) better associate obesity with the health risk factor(19). WC and WHR are shown to be associated with an increased risk of all-cause of obesity-related mortality inducing ischemic heart diseases(20). In population, the type of fat distribution is related to the development of an obesity-related complication(21, 22). Men have more lean mass with a central distribution of adipose, whereas women have a higher overall proportion of adiposity with the peripheral distribution(23). Abdominal obesity is strongly associated with the development of insulin resistance and hyperglycemia in compere to general obesity (21, 24, 25).

Diabetes is a metabolic disorder with two primary types, 1 and 2. Type 2 is a heterogeneous disorder characterized by insulin resistance(26, 27) in the presence of pancreatic beta-cells failure to produce sufficient insulin to meet the essential need(26, 28). Diagnosis of D.M. is made as an 8hr post fasting blood glucose> 126mg/dl or a 2-hour postprandial blood glucose> 200 mg/dl(29). D.M. results from an interaction between

the subject genetic makeup and his/her environment. Lifestyle and obesity are among the principle environment factor that enhances the risk of developing diabetes.

2. Epidemiology:

Today obesity dependent diabetes is one of the significant health challenges of the 21st century. Over the past years, the prevalence of obesity has increased worldwide to the pandemic proportion(30, 31). The international obesity task force has estimated that worldwide more than 312 million adults are obese(32). The total number of overweight population worldwide is projected to increase from 937 million in 2005 to 1.35 billion in 2030. In contrast, the number of obese individuals is expected to grow from 396 million to 573 million(33). Overweight and obesity are projected to cost $860 billion to $956 billion (15.8%-17.6% of total health cost) by 2030(34).developed nations are failing badly in their attempts to control the obesity epidemic(35). Some study shows the increasing prevalence of obesity coincides with improved economy and wealth of the country(36). The obesity rate was tripling in developing countries during the past 20 years(37), especially in urban areas because of several factors, including a shift from rural to the urban lifestyle and decreased physical activities(38).

Recent data from the national diabetes statistics report (2017) indicates that 87.5% of adults with diabetes are overweight/obese(39). A report suggested that there were 171 million people with diabetes in 2000; 285 million people currently have diabetes and predicted to be 366 million people by 2030(40). The most recent prediction is that in 2040 there will be 642 million diabetic people worldwide(41). The global expenditure for prevention and treatment is projected to exceed $490 billion by 2030(42). Geographically the incidence of diabetes is expected to rise by 32% in Europe and 72% in the USA by 2030. However, the most dramatic projected increase in diabetes incidence (>150%) is predicted in the middle east, sub-urban Africa, Latin America(37, 40), and Asia as a hot spot mainly because of rapid economic development, urbanization and lifestyle change(43). There are significant differences in the risk of type 2 DM due to obesity among the ethnic group (18, 44)where US black, American Indians, Hispanics, and pacific islanders having a higher propensity for developing diabetes(39). Diabetes develops in Asians people at a lower BMI(25kg/m2) compared with people of European(30kg/m2) and African-Caribbean (27kg/m2)(45).

3. Pathological factors linking obesity to diabetes:

90 % of type 2 D.M is attributed to excess weight(46). A term lipotoxicity is used to explain the role of obesity in promoting insulin resistance, which finally leads to type 2 D.M progression(47). In an obese person, it results due to an increase in products of adipose tissues, including NEFA, glycerol, hormones, and pro-inflammatory cytokines(48). Now we shall see these factors individually and their contribution to disease progression.

3.1 NEFA (non-esterified fatty acids):

Increased TG in obesity increases the proportion of adipocytes that finally become more resistant to the anti-lipolytic effect of insulin, resulting in the release of a higher amount of fatty acid in circulation(46). The level of NEFA is elevated in obese people(49), and elevated NEFA is associated with insulin resistance observed

in both obesity and D.M(50). Some of these following factors have shown to result in subsequent metabolic dysfunction leading to type 2 D.M:

- NEFA reduces glucose uptake by adipocytes and liver and promotes hepatic glucose output to cause hyperglycemia(51).
- The energy produced by fatty acid oxidation is utilized by the liver for gluconeogenesis that further increases blood glucose level(47).
- NEFA metabolites impede insulin-stimulated glucose transport in muscle and inhibit normal suppression of gluconeogenesis(47).
- Increased fatty acid metabolites like diacylglycerol(52), ceramides, fatty acyl-coenzyme A, in turn, activates serine/threonine kinase cascade leading to serine/threonine phosphorylation of insulin receptor substrate 1 and 2(53). A reduced ability of these molecules to activate phosphatidylinositol-3-OH kinase(PI(3)K) results in diminished insulin receptor signalling (53).

3.2 Adipocytes hormones:

Adipose tissue is not only a calorie storage organ. It is also an active endocrine organ and releases several protein hormones that regulate energy homeostasis and modulate metabolism. Adiponectin, leptin, resistin, lipocalin-2, TNF- α, IL-6 are some of those factors which play a crucial role in developing insulin resistance and type 2 D.M in obesity(48, 54).

Adiponectin function as anti-inflammatory factor and insulin sensitizer(48). Hence it constitutes as an essential natural defence mechanism against type 2 D.M. it enhances insulin sensitivity primarily by inhibition of hepatic glucose production(55) and by stimulating fatty acid oxidation in an AMP-activated protein kinase(AMPK) and peroxisome proliferator-activated receptor –α (PPAR- α) dependent manner(48). Studies have shown that increased adipocytes deposition leads to a marked reduction in adiponectin level in the obese diabetic patient(56), and also adiponectin level negatively correlates with insulin resistance(57, 58) and high incident of type 2 D.M(59). visceral adipose tissue has high hyper-lipolytic activity. So they have high secretion of these hormones, and since visceral adipose tissue drains directly into hepatic portal veins, such exposure of the liver to the high concentration of metabolites and adipokines may increase cardiometabolic risk(60).

Leptin is another hormone primarily secreted by adipose tissue. It increases insulin sensitivity and muscle fatty acid oxidation(61). Leptin deficiency leads to uncontrolled food intake, obesity, and other metabolic disorders(62). The plasma level of leptin correlates directly with adipose tissue mass, obesity, and insulin resistance(63). Many studies showed that in obesity, there is a positive correlation between adipose-insulin resistance and leptin(64, 65). Hence elevated leptin level explains the leptin resistance, which is also a risk factor for obesity(62).

Resistin is another peptide hormone that is shown to be involved in the link between insulin resistance and obesity(66). Decreased resistin is involved with improved insulin resistance(66). A published meta-analysis showed a significant increase in circulating visfatin levels in the overweight and obese subject, another adipocyte hormone, concluding a strong association between visfatin and insulin resistance(67).

Retinol-binding protein-4 (RBP4) is also an adipokine that has been implicated in inducing insulin resistance through phosphatidylinositol-3-OH kinase (PI(3)K) signalling in muscle and enhanced expression of gluconeogenic enzyme phosphoenolpyruvate carboxykinase in the liver through retinol-dependent mechanism(68).

3.3 Pro-inflammatory cytokines:

Although the mechanism of pro-inflammatory cytokines inducing insulin resistance and diabetes is unclear however the release of TNF- α, IL-6, monocyte chemoattractant protein-1(MCP-1) and additional product of macrophage and other cells that populate adipose tissue has a role in the development of insulin resistance and type 2 D.M(69). Furthermore, CRP (C-reactive protein), induces phosphorylation of IRS-1 on two separate residues (Ser307 and Ser612) in L6 myocytes. This ultimately inhibits the insulin-signalling pathway via JNK (c-JunN-terminal kinase) and ERK1/2 (extracellular-signal-regulated kinase 1/2), and eventually impairs insulin-stimulated glucose uptake, GLUT4 (glucose transporter4) translocation and glycogen synthesis, as mediated by the IRS-1/PI3K/protein kinase B (also known as Akt)/GSK-3 (glycogen synthase kinase-3) pathway(70). TNF- α and IL-6 also play a crucial role in the genesis of endothelial dysfunction inducing endothelial expression of chemokines (IL-1) and adhesion molecules (ICAM-1, VCAM-1, and P-selectin) which are central to the early phase of the atherogenesis process(71).

Recently, Taylor et al. proposed the 'twin cycle hypothesis' to better explain the etiology of T2DM in obese patients(28, 72). According to which, hepatic rather than muscle insulin resistance is involved in the occurrence of hyperglycemia and overt diabetes in obese patients.

The etiologic mechanism proposed by Pories and Pories et al. for the development of T2DM in obese patients shows the role of incretin hormones. It implies that metabolic deterioration in obesity progress as a result of an overstimulation of incretins induced by overeating, leading to hyperinsulinemia and insulin resistance(73).

4. Genetic implications:

Along with the multiple lifestyle-based factors linking obesity to diabetes, there is also evidence for a strong genetically-based association between obesity and diabetes in populations(74). Now, epigenetic pathways and early-life events have received substantial attention in relation to type 2 diabetes(75).

Adiponectin is encoded by the *ADIPOQ* gene(76). There are 149 variants identified in this gene that result in reduced adiponectin level(77). These variations have shown to affect insulin sensitivity in obese diabetic patients(78)and show a significant association with increased BMI(79).

Peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor protein, is of central interest in the pathogenesis of diabetes and obesity.

Pro12Ala polymorphism *in the PPAR-γ* gene is associated with an increased risk of developing diabetes(80). Genome-wide association studies (GWAS) identified several gene variants associated with T2DM. For BMI variability, the *FTO* gene was statistically the most potent genetic factor related to obesity(81). *CDKAL1*

SNP gene mutation impairs beta-cell function without affecting insulin sensitivity(82), whereas variants in the insulin-like binding protein 2 (*IGF2BP2*) gene are associated with T2DM in several ethnic groups(83).

Several genes related to β-cell dysfunction have been identified. Such as hepatocyte nuclear factor-4α and 1α, E23K polymorphism in the islet ATP-sensitive potassium channelKir6.2, and two non-coding single-nucleotide polymorphisms in the transcription factor 7-like 2(84).

Recently, Work is going on in many candidate genes, including calpain 10, PPAR-γ co-activator 1 (*PGC1*), and the glucose transporter GLUT2(84). Genetic Investigation of Anthropometric Traits investigators has also identified hundreds of common novel variants associated with weight and BMI, waist circumference, waist to hip circumference ratio, height, and macronutrient intake. In a similar analysis, a genetic risk score interacted with fried food consumption, showing that frequent use of fried food magnified genetic risk(85).In addition, the Health Professionals Follow-up Study showed genetic risk interacted with television viewing (86), physical activity, and, most recently, vitamin B intake(87)on obesity risk.

5. Etiology and efforts to battle obesity-linked diabetes:

In the past few years, over nutrition had emerged as a more significant health problem compared to undernutrition. Which means more people are dying from overweight and obesity then underweight(88). There is a broad consensus that change in the global food system(88, 89) combined with a sedentary lifestyle(90)seems to be the leading cause of the worldwide rise in obesity prevalence over past 50 years.

Environmental factors are one of the significant responsible reason for the modern-day epidemic of obesity and type 2DM. They include increased fat consumption, sedentary behaviour with decreased energy expenditure(91), biological factors (low quality sleep, psychological factors, weight stigma, discrimination) (92)and poor nutrition during an early postnatal period. The later alters metabolism, resulting in a tissue adaptation that favours the storage of food (93). The result of these environmental changes is a deleterious interaction with genes that finally predispose to the development of obesity and type 2 DM.

Obesity linked to diabetes is a preventable disease. Lifestyle intervention(94), weight loss with diet and exercise are the first-line strategy for maintaining homeostatic mechanism before drug intervention becomes inevitable. Weight loss therapy is recommended for a patient with BMI of 30 kg/m2 or higher and a patient with BMI between 25 and 29.9kg/m2 or high-risk WC and two or more risk factors(19).

Diet should consist of low calories, low-fat food with a calorie goal of 1000-1200 kcal/day for most women and 1200 to 1600 kcal/day for men(19). it also should include a high intake of dietary fibre, particularly of the soluble type, which has shown to improve glycemic control and maintain lower plasma lipid concentration. Regular physical activity should be encouraged, which has demonstrated enhanced insulin sensitivity(95), maintain weight(19) and decrease the risk of developing diabetes.

Public health initiative will be required to make interventions aimed at motivating behaviour changes like health promotion, encourage and facilitate exercise. Enhanced collaboration between government, private sector and community institution should be promoted to provide a healthy environment through a healthy lifestyle. The intervention also should be targeted for food industries, restricting marketing of obesogenic

foods, particularly aiming at children(88, 96). Research related to nutrition and risk factors of obesity should be conducted more often.

Recently bariatric/metabolic surgery has shown a dramatic effect on glycemic control(97) and play an essential role in both treatment and prevention of type 2 DM. Patient with a BMI over 40 kg/m2 as well as those with BMI over 35 and co-morbidities, who failed to obtain and maintain significant weight reduction through non-surgical means are submitted to bariatric surgery. It results in clinical remission of diabetes in 64.83% of patients (98)and even has found to be more effective than conventional medical therapy in several control trials(97, 99). bariatric surgery has revelled that beyond weight loss and food restriction, other mechanisms such as incretins system, change in bile acid composition with flow and modification of gut bacteria can be activated by rearrangement of GI tract, that is possibly involved in remission of type 2 DM(100). further research has to be done in this field of subject.

CONCLUSION

Obesity is expanding health care crisis around the world. It is associated with an increased risk of developing type 2 DM. Excessive weight results in an earlier onset of type 2 DM in genetically predisposed individuals. We saw how visceral adiposity and insulin resistance that are distinctive clinical features of type 2 DM are strictly associated with the pathological factors like NEFA, hormones and pro-inflammatory cytokines secreted by adipocytes. Current non-surgical weight loss therapy consists of lifestyle modification and medications. In contrast, bariatric surgery has been shown to be safe and very efficient in achieving and maintaining weight loss as well as treating the medical co-morbidities of obesity.

Limiting weight gain and obesity even in the face of genetic predisposition is possible through a healthy diet, regular physical activity and other positive lifestyle interventions, which has shown to be the best preventive measure against chronic mortality and morbidity. However, an integrated approach is needed for its prevention and recognition of heterogeneity between obesity and type 2 DM. Further research needs to be directed at the understanding of the potential role of determinants such as maternal environment, early life factors, genetic associations, as well as changing trends in global demography, that will help to shape the disease prevention programs.

Abbreviations:

BMI: Body mass index

Type2 DM: Type 2 diabetes mellitus

TG: Triglycerides

NEFA: non-esterified fatty acids

REFERENCES

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81.
2. Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017;18(7):715-23.
3. Fontaine K, Redden D, Wang C, Westfall A, Allison D. Years of Life Lost Due to Obesity. JAMA : the journal of the American Medical Association. 2003;289:187-93.
4. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010;363(23):2211-9.
5. Masuo K, Rakugi H, Ogihara T, Esler MD, Lambert GW. Cardiovascular and renal complications of type 2 diabetes in obesity: role of sympathetic nerve activity and insulin resistance. Curr Diabetes Rev. 2010;6(2):58-67.
6. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med. 2001;161(13):1581-6.
7. Bray GA. Medical consequences of obesity. The Journal of Clinical Endocrinology & Metabolism. 2004;89(6):2583-9.
8. Yang W, Dall T, Beronjia K, Lin J, Semilla AP, Chakrabarti R, et al. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018;41:917-28.
9. Raz I. Complex impact of obesity on type 2 diabetes. Isr Med Assoc J. 2005;7(6):402-3.
10. Jiang X, Ma H, Wang Y, Liu Y. Early life factors and type 2 diabetes mellitus. Journal of diabetes research. 2013;2013.
11. Abdullah N, Attia J, Oldmeadow C, Scott RJ, Holliday EG. The architecture of risk for type 2 diabetes: understanding Asia in the context of global findings. Int J Endocrinol. 2014;2014.
12. Ogedengbe SO, Ezeani IU. Profile of metabolic abnormalities seen in patients with type 2 diabetes mellitus and their first degree relatives with metabolic syndrome seen in Benin City, Edo state Nigeria. Journal of Diabetes & Metabolic Disorders. 2014;13(1):61.
13. Sibai AM, Costanian C, Tohme R, Assaad S, Hwalla N. Physical activity in adults with and without diabetes: from the 'high-risk'approach to the 'population-based'approach of prevention. BMC Public Health. 2013;13(1):1002.
14. Lindström J, Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. Diabetes Care. 2003;26(3):725-31.
15. Connolly V, Unwin N, Sherriff P, Bilous R, Kelly W. Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of type 2 diabetes mellitus in deprived areas. J Epidemiol Community Health. 2000;54(3):173-7.

16. Organization WH. Obesity: preventing and managing the global epidemic: World Health Organization; 2000.
17. IASO W. IOTF. The Asia Pacific Perspective: Redefining Obesity and Its Treatment. Health Communications Australia Pty Limited. 2000.
18. Who EC. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet (London, England). 2004;363(9403):157.
19. NIH N, NHLBI N. The practical guide identification, evaluation, and treatment of overweight and obesity in adults. NIH Publication Number DO-4084; 2000.
20. Seidell J. Waist circumference and waist/hip ratio in relation to all-cause mortality, cancer and sleep apnea. Eur J Clin Nutr. 2010;64(1):35-41.
21. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk—a review of the literature. Eur J Clin Nutr. 2010;64(1):16-22.
22. Oliveira A, Rodriguez-Artalejo F, Severo M, Lopes C. Indices of central and peripheral body fat: association with non-fatal acute myocardial infarction. International journal of obesity. 2010;34(4):733-41.
23. Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. Gend Med. 2009;6:60-75.
24. Björntorp P. Metabolic implications of body fat distribution. Diabetes Care. 1991;14(12):1132-43.
25. Miyazaki Y, Glass L, Triplitt C, Wajcberg E, Mandarino LJ, DeFronzo RA. Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus. American Journal of Physiology-Endocrinology and Metabolism. 2002;283(6):E1135-E43.
26. Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J. 2008;29(24):2959-71.
27. Mirmiran P, Bahadoran Z, Azizi F. Functional foods-based diet as a novel dietary approach for management of type 2 diabetes and its complications: A review. World J Diabetes. 2014;5(3):267.
28. Taylor R. Type 2 diabetes: etiology and reversibility. Diabetes Care. 2013;36(4):1047-55.
29. Association AD. Standards of medical care in diabetes—2017 Diabetes care.[Internet] 2017 Jan [citado 23 Feb 2017]; 40 (Supl1).
30. Collaboration NRF. Worldwide trends in children's and adolescents' body mass index, underweight, overweight and obesity, in comparison with adults, from 1975 to 2016: a pooled analysis of 2, 416 population-based measurement studies with 128.9 million participants. Lancet. 2017;390:2627-42.
31. Yanovski JA. Trends in underweight and obesity—scale of the problem. Nature Reviews Endocrinology. 2018;14(1):5-6.
32. Haslam D, James W. Obesity Lancet, 366 (9492), 1197–1209. Health Physics Society (2009) Online, availableat: www hps org/publicinformation/ate/q535 html. 2005.
33. Kelly T, Yang W, Chen C-S, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. International journal of obesity. 2008;32(9):1431-7.

34. Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. Obesity. 2008;16(10):2323-30.
35. Gluckman PD, Hanson M, Zimmet P, Forrester T. Losing the war against obesity: the need for a developmental perspective. Sci Transl Med. 2011;3(93):93cm19-93cm19.
36. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: shaped by global drivers and local environments. The Lancet. 2011;378(9793):804-14.
37. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world—a growing challenge. New England journal of medicine. 2007;356(3):213-5.
38. Shamseddeen H, Getty JZ, Hamdallah IN, Ali MR. Epidemiology and economic impact of obesity and type 2 diabetes. Surgical Clinics. 2011;91(6):1163-72.
39. Control CfD, Prevention. National diabetes statistics report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services. 2017;20.
40. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047-53.
41. Atlas D. International diabetes federation. IDF Diabetes Atlas, 7th edn Brussels, Belgium: International Diabetes Federation. 2015.
42. Unwin N, Gan D, Whiting D. The IDF Diabetes Atlas: providing evidence, raising awareness and promoting action. Diabetes Res Clin Pract. 2010;87(1):2-3.
43. Nanditha A, Ma RC, Ramachandran A, Snehalatha C, Chan JC, Chia KS, et al. Diabetes in Asia and the Pacific: implications for the global epidemic. Diabetes Care. 2016;39(3):472-85.
44. Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). The American journal of clinical nutrition. 2007;86(2):353-9.
45. Tillin T, Sattar N, Godsland I, Hughes A, Chaturvedi N, Forouhi N. Ethnicity-specific obesity cut-points in the development of Type 2 diabetes–a prospective study including three ethnic groups in the United Kingdom. Diabet Med. 2015;32(2):226-34.
46. Montague CT, O'Rahilly S. The perils of portliness: causes and consequences of visceral adiposity. Diabetes. 2000;49(6):883-8.
47. Day C, Bailey CJ. Obesity in the pathogenesis of type 2 diabetes. The British Journal of Diabetes & Vascular Disease. 2011;11(2):55-61.
48. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes. 2006;55(6):1537-45.
49. Karpe F, Dickmann JR, Frayn KN. Fatty acids, obesity, and insulin resistance: time for a reevaluation. Diabetes. 2011;60(10):2441-9.
50. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840-6.

51. Thévenod F. Pathophysiology of diabetes mellitus type 2: roles of obesity, insulin resistance and β-cell dysfunction. Diabetes and Cancer. 19: Karger Publishers; 2008. p. 1-18.
52. Parekh DB, Ziegler W, Parker PJ. Multiple pathways control protein kinase C phosphorylation. The EMBO journal. 2000;19(4):496-503.
53. Shulman GI. Cellular mechanisms of insulin resistance. The Journal of clinical investigation. 2000;106(2):171-6.
54. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nature reviews immunology. 2011;11(2):85.
55. Lihn A, Pedersen SB, Richelsen B. Adiponectin: action, regulation and association to insulin sensitivity. Obes Rev. 2005;6(1):13-21.
56. Alfadda AA. Circulating adipokines in healthy versus unhealthy overweight and obese subjects. Int J Endocrinol. 2014;2014.
57. Yamamoto Y, Hirose H, Saito I, Tomita M, Taniyama M, Matsubara K, et al. Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. Clin Sci. 2002;103(2):137-42.
58. Turer A, Scherer P. Adiponectin: mechanistic insights and clinical implications. Diabetologia. 2012;55(9):2319-26.
59. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2009;302(2):179-88.
60. Klöting N, Stumvoll M, Blüher M. The biology of visceral fat. Internist (Berl). 2007;48(2):126-33.
61. Havel PJ. Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. Diabetes. 2004;53(suppl 1):S143-S51.
62. Morris DL, Rui L. Recent advances in understanding leptin signaling and leptin resistance. American Journal of Physiology-Endocrinology and Metabolism. 2009;297(6):E1247-E59.
63. Adams-Huet B, Devaraj S, Siegel D, Jialal I. Increased adipose tissue insulin resistance in metabolic syndrome: relationship to circulating adipokines. Metabolic syndrome and related disorders. 2014;12(10):503-7.
64. Jialal I. Adipose tissue dysfunction in nascent metabolic syndrome. J Obes. 2013;2013.
65. Jialal I, Devaraj S, Kaur H, Adams-Huet B, Bremer AA. Increased chemerin and decreased omentin-1 in both adipose tissue and plasma in nascent metabolic syndrome. The Journal of Clinical Endocrinology & Metabolism. 2013;98(3):E514-E7.
66. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature. 2001;409(6818):307-12.
67. Chang YH, Chang DM, Lin KC, Shin SJ, Lee YJ. Visfatin in overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases: a meta-analysis and systemic review. Diabetes Metab Res Rev. 2011;27(6):515-27.

68. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature. 2005;436(7049):356-62.
69. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology. 2004;145(5):2273-82.
70. D'Alessandris C, Lauro R, Presta I, Sesti G. C-reactive protein induces phosphorylation of insulin receptor substrate-1 on Ser 307 and Ser 612 in L6 myocytes, thereby impairing the insulin signalling pathway that promotes glucose transport. Diabetologia. 2007;50(4):840-9.
71. Esposito K, Nicoletti G, Giugliano D. Obesity, cytokines and endothelial dysfunction: a link for the raised cardiovascular risk associated with visceral obesity. J Endocrinol Invest. 2002;25(7):646-9.
72. Taylor R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. Diabetologia. 2008;51(10):1781-9.
73. Pories WJ. Why does the gastric bypass control type 2 diabetes mellitus? Obes Surg. 1992;2(4):303-13.
74. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. The lancet Diabetes & endocrinology. 2014;2(1):56-64.
75. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. New England Journal of Medicine. 2008;359(1):61-73.
76. Mackevics V, Heid IM, Wagner SA, Cip P, Doppelmayr H, Lejnieks A, et al. The adiponectin gene is associated with adiponectin levels but not with characteristics of the insulin resistance syndrome in healthy Caucasians. European Journal of Human Genetics. 2006;14(3):349-56.
77. Jungtrakoon P, Plengvidhya N, Tangjittipokin W, Chimnaronk S, Salaemae W, Chongjaroen N, et al. Novel adiponectin variants identified in type 2 diabetic patients reveal multimerization and secretion defects. PLoS One. 2011;6(10).
78. Siitonen N, Pulkkinen L, Lindström J, Kolehmainen M, Eriksson JG, Venojärvi M, et al. Association of ADIPOQ gene variants with body weight, type 2 diabetes and serum adiponectin concentrations: the Finnish Diabetes Prevention Study. BMC Med Genet. 2011;12(1):5.
79. Enns JE, Taylor CG, Zahradka P. Variations in adipokine genes AdipoQ, Lep, and LepR are associated with risk for obesity-related metabolic disease: the modulatory role of gene-nutrient interactions. J Obes. 2011;2011.
80. Tönjes A, Stumvoll M. The role of the Pro12Ala polymorphism in peroxisome proliferator-activated receptor γ in diabetes risk. Curr Opin Clin Nutr Metab Care. 2007;10(4):410-4.
81. Loos RJ, Yeo GS. The bigger picture of FTO—the first GWAS-identified obesity gene. Nature Reviews Endocrinology. 2014;10(1):51.
82. Pascoe L, Tura A, Patel SK, Ibrahim IM, Ferrannini E, Zeggini E, et al. Common variants of the novel type 2 diabetes genes CDKAL1 and HHEX/IDE are associated with decreased pancreatic β-cell function. Diabetes. 2007;56(12):3101-4.

83. Ng MC, Park KS, Oh B, Tam CH, Cho YM, Shin HD, et al. Implication of genetic variants near TCF7L2, SLC30A8, HHEX, CDKAL1, CDKN2A/B, IGF2BP2, and FTO in type 2 diabetes and obesity in 6,719 Asians. Diabetes. 2008;57(8):2226-33.
84. Barroso I. Genetics of type 2 diabetes. Diabet Med. 2005;22(5):517-35.
85. Qi Q, Chu AY, Kang JH, Huang J, Rose LM, Jensen MK, et al. Fried food consumption, genetic risk, and body mass index: gene-diet interaction analysis in three US cohort studies. BMJ. 2014;348:g1610.
86. Qi Q, Li Y, Chomistek AK, Kang JH, Curhan GC, Pasquale LR, et al. Television watching, leisure time physical activity, and the genetic predisposition in relation to body mass index in women and men. Circulation. 2012;126(15):1821-7.
87. Huang T, Zheng Y, Qi Q, Xu M, Ley SH, Li Y, et al. DNA methylation variants at HIF3A locus, B-vitamin intake, and long-term weight change: gene-diet interactions in two US cohorts. Diabetes. 2015;64(9):3146-54.
88. Blüher M. Obesity: global epidemiology and pathogenesis. Nature Reviews Endocrinology. 2019;15(5):288.
89. Roberto CA, Swinburn B, Hawkes C, Huang TT, Costa SA, Ashe M, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. The Lancet. 2015;385(9985):2400-9.
90. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. JAMA. 2003;289(14):1785-91.
91. Hebebrand J, Holm J-C, Woodward E, Baker JL, Blaak E, Schutz DD, et al. A proposal of the European association for the study of obesity to improve the ICD-11 diagnostic criteria for obesity based on the three dimensions etiology, degree of adiposity and health risk. Obesity facts. 2017;10(4):284-307.
92. Ramos Salas X, Alberga A, Cameron E, Estey L, Forhan M, Kirk S, et al. Addressing weight bias and discrimination: moving beyond raising awareness to creating change. Obes Rev. 2017;18(11):1323-35.
93. Hales CN, Barker D. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Int J Epidemiol. 2013;42(5):1215-22.
94. Herman WH. Response to Comment on Inzucchi et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38: 140–149. Diabetes Care. 2015;38(9):e143-e.
95. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med. 1998;49(1):235-61.
96. Kleinert S, Horton R. Rethinking and reframing obesity. The Lancet. 2015;385(9985):2326-8.
97. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. New England Journal of Medicine. 2012;366(17):1577-85.
98. Dixon JB. Obesity and diabetes: the impact of bariatric surgery on type-2 diabetes. World J Surg. 2009;33(10):2014.

99. Müller-Stich BP, Senft JD, Warschkow R, Kenngott HG, Billeter AT, Vit G, et al. Surgical versus medical treatment of type 2 diabetes mellitus in nonseverely obese patients: a systematic review and meta-analysis. Ann Surg. 2015;261(3):421-9.

100. Catoi AF, Parvu A, Muresan A, Busetto L. Metabolic Mechanisms in Obesity and Type 2 Diabetes: Insights from Bariatric/Metabolic Surgery. Obes Facts. 2015;8(6):350-63.