



Pathology of Diabetes Mellitus and the Association of Physical Activity, Nutritional Status, and Related Factors with Diabetes Mellitus Development: A Literature Review

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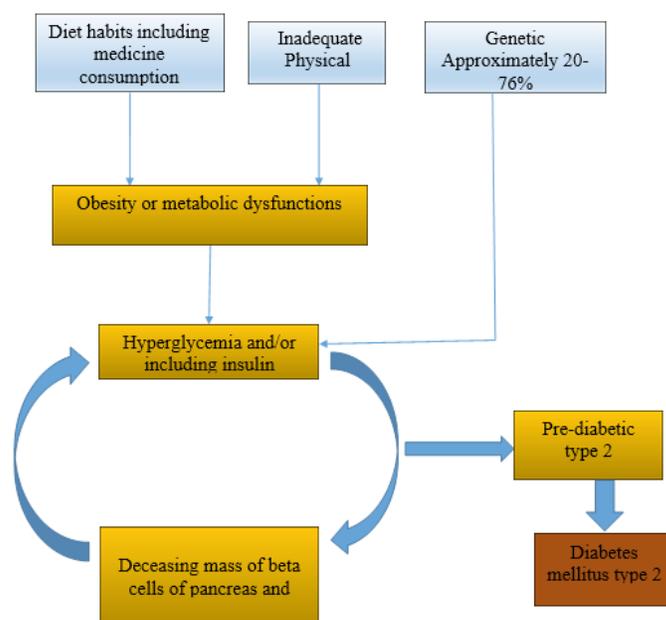
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Abstract

Diabetes mellitus has been occurred at high prevalence worldwide, WHO estimated that 408 million people have been diagnosed with diabetes in 2014. The disease is non-communicable disease which indicated that lifestyle and food consuming behavior are high level of association with diabetes development. Repeated researches have been concluded that physical activities and nutritional level of non-diabetic people contribute to the development of diabetes mellitus but the clarified picture of physical activity and nutrition elements in the diabetes progress has not been systematic reviewed, some inconsistency result from different research has been made. By reviewing articles of this issue, we concluded that physical activity and nutrition might contribute to diabetes development by permanently changing the carbohydrate metabolism leading to diabetes of both type 1&2. Modifying physical activity and nutrition of diet in pre-diabetic period reduce significant



Graphical Abstract.

Keywords: Nutritional Diet; Pathology of Diabetes; Physical Activity

Introduction

Diabetes mellitus has serious consequences to global health. WHO reported that the number of cases of diabetes has been dramatically increased from 108 million to 408 million in period of 1980-2014 and the prevalence of diabetes among population over 18 years old is 8.5% which is high compared to other non-communicable diseases occur [1]. Diabetes is mentioned such as metabolic disorder, diabetes type 2 is situation of body could not control their blood glucose because of insensitive of insulin and/or the level of produced insulin is not adequate enough in mechanism of transferring glucose into the cells, therefore, leading to high level of glucose in bloodstream. Patients need to take medicine to normalize their blood glucose and reduce the opportunity of complications. There are many factors related to the progression of diabetes 2-type such as genetic, obesity, physical activity and diet. Obesity consider is a symptom of some metabolic disorder such as diabetes 2-type. The obese adipocytes promote to release, IL-6, resist in which is cause of hyperglycemia and also limit the amount of adiponectin which is in charge of insulin sensitizer. Studies has been showed the association between diabetes with some cancers such as liver, pancreas, endometrium [2]. Physical activity and nutritional diet are important role in prevention and combating with metabolic diseases such as diabetes mellitus type 2 [3]. Lacking of physical activity could promote the body to have more obese adipocytes and making serious health issue [4]. There is a clear evidence that obese adipocytes increasingly secrete hormone, cytokines and some substance which dysfunctional cell proliferation is and leading to metabolic disorder or even cancers [5]. Some recommended guideline for food intake and physical activity for risk group of diabetes and pre-diabetes mellitus groups [3] but still slacking of condition of physical activity and food consuming in diabetic patients. People with diabetes mellitus should avoid of consuming too much glucose such as rice and processed foods which help rapidly increasing level of blood sugar and could promote the progression of diabetes more severely, diabetic patients also need to avoid consume a lot of salt, red meat to avoid the metabolism disorder. Vegetable and fruit are considered as good food to consume for people with diabetes. Diabetes mellitus patients need to have regular plan for physical activates in order to combat with diabetes as well as its complications. Adequate physical activity could support the metabolism and support the treatment of diabetes.

Physical activity and nutritional diet affect to health condition of diabetic patients, therefore, prograded education training for diabetes type 2 has been implemented in some developed countries such as Australian which has been proved that increasing the level of diabetes knowledge and physical activity, changing diet

habit of the patients [6] but some developing countries lacking of educational campaign as well as not enough fundable campaign to combat with diabetes type 2 is reason why people do not understand of how they modify physical activity and diet if they have diabetes mellitus and how the impact of physical activity and diet affect their health. In this review, we will provide the answer of these questions.

The Global Epidemiology of Diabetes

Globally, the diabetes cases have been reported increased from 108 million in 1980 to 422 million in 2014 which indicated approximately 8.5% of total population [1]. The trend of diabetes has been dramatically changed in term of epidemiology which is switching from developed countries to developing countries. Statistically, the mortality of diabetes in 2012 is 1.5 million which was eight leading cause of death among both sexes and fifth in female fatality [1]. In Western Pacific Region including Vietnam, the cases of death due to high blood glucose increased from 490.000 to 944.000 during the period of 2000-2012 [1].

Pathology of Diabetes

Diabetes could be classified as chronic inflammation disease [7]. There are 2 types of diabetes which are type1 and type2. Pancreas is an critical organ located in the abdomen with two main functions of exocrine and endocrine and plays important role in diabetes development; pancreas release enzymes into digestion system to promote the digestion of proteins, carbohydrates, the organ also secretes insulin and glucagon to regulate blood sugar by hormones, insulin hormone secreted by beta cell of islet cells within the pancreas and glucagon hormone released by alpha cells in pancreatic islets cells. Pancreas plays central role in development of 2types of diabetes.

Glucagon secreted when the blood glucose is very low particularly during the meal to promote the release of glucose into blood stream from adipocytes, liver cells, with opposite pathway of insulin, insulin increasingly secreted when level of sugar in blood is high and speed up the transportation of glucose into cells. This hormone plays important role in mechanism of maintenance the level of glucose in blood stream by transferring glucose into muscle cells; adipocytes and liver, the glucose in this process will be stored with the forms of glycogen or triglycogen. The level of insulin in blood stream is inversely with the amount of glucose in blood stream. High level of glucose in blood stream which is called hyperglycemia causing many consequences and also be considered as complications of diabetes such as dysfunction of kidney including some kidney diseases such as kidney failure or etiology issues such as loss of vision or stroke. The types of diabetes are classified by the reasons of not properly secreting insulin of pancreas. Type 1 diabetes is caused by destruction of β pancreatic

islet cells and type2 caused by dysfunction of β pancreatic islet cells. In type1 diabetes, the pancreas completely disables secret insulin but in the type2, the level of insulin secreted by pancreas reduces significantly. Type 1 diabetes caused by destruction of insulin production because T-cell lymphocytes destroys pancreatic beta cells therefore pancreas disability secret insulin to modify the level of blood glucose, the pathology of the type 1 is ambiguous but this is the result of interacting between genetic factor and environment and almost occurs in children and adolescent [8] but sometime this disease occurs in people lately of thirties and early forties [5], there are strong association between type 1 diabetes some diseases in immune system such as Hashimoto's thyroiditis and Graves' disease, autoimmune gastritis [9,10] .

There are approximately 10% of all diabetes case are type1 diabetic mellitus. Type2 of diabetes is different with type1, the insulin still secreted by pancreas but not working properly due to 2 reasons: (1) the level of insulin in blood stream is not adequate enough to control blood glucose due to dysfunctional pancreas, a decrease of pancreas to nearly 60% has been observed in patients with type 2 diabetes [11] (2) or the insensitive of insulin to cell (insulin resistance) leading to dysfunctional process of beta cell of pancreas islet cells [12], reducing the level of insulin secretion, therefore, the glucose in bloodstream could not enter into cell leading to high level of blood glucose and causing diabetes, researchers has been indicated that in obese body, obese adipocytes tend to be lack of sensitivity of insulin therefore obesity situation could have very significant role in term of insulin insensitive [13]. The prevalence of diabetes type 2 is dominant comparing to type 1 rate which occur almost 90% of all diabetes cases [1]. The limited knowledge of diabetes suggests that type1 could not be preventable, but patients require of using medicine during their lifetime, type 2 diabetes could be prevented and controlled by modify lifestyle and nutritional diet in long term including energy balanced and physical activity programed [1]. The consequence of diabetes is both in short-term and long-term such as reduction of muscle mass [14,15], cardiovascular diseases, loss of vision, kidney failure or even premature death [16].

The Important Role of Immune System in Diabetes Pathological Development

The immune imbalance plays very important role in development of carbohydrate metabolism diseases such as type 2 mellitus by increasingly level of Th17-lymphocytes and some pro-inflammatory factors such as TNF-alpha, IL-6, leptin, IL-1, IL-1R alpha, IL-8, IL-18, MCP-1, MIF, TGF-beta [17,18]. The level of anti-inflammatory substance is decreased such as adiponectin, IL-10 [18], adiponectin enhance ceramide catabolism by AdipoR1 and AdipoR2, study observed that when hepato-cellular ceramide levels are high leading to decreasing of insulin sensitivity [19] low level of adiponectin is prognosis of diabetic situation in gestational

period [20]. Pro-inflammatory substances such as Tumor necrosis factor alpha (TNF- α) which is pro-inflammatory cytokine involved in systematic inflammation and acute phase reaction plays critical role in diabetes type 2 development by promoting the insulin resistance [21], the level of this cytokine increases in obesity because of the overproduced secretion of TNF- alpha by obese white adipocytes [22] and plays important role in development of insulin resistance which is prohibiting the expression of many proteins such as insulin receptor, IRS-1, GLUT4 are needed for insulin stimulating on transporting glucose in adipocytes [23,24], this process lead to promoting the inhibition of the insulin receptor and lead to insulin resistance . The association between diabetes and immune system open the promising future of treating diabetes type2 with immunomodulatory treatment may improve beta-cell function, reduce the insulin resistance [25].

The Associated Factors of Diabetes

The Directed Factors of Diabetes

Obesity vs. type 1 diabetes

The association between diabetes type 1 and obesity has been investigated by Baum during 1970s, theory in this research suggested that due to over feeding and dysregulating hormone in pre-diabetic type1 promote the development of diabetes type 1 [26,27].

Obesity vs. type 2 diabetes

The role of obesity in progression of diabetes mellitus 2 is significant and has been proved in several researches. The obese adipocytes secrete many substances which are proved have role in mechanism of leading to insulin resistance such as free fatty acids, resistin, leptin, cytokines, glycerol, hormones and some pro-inflammatory cytokines, obese adipocytes are more insensitive with insulin than normal adipocytes, especially in central fat because visceral adipocytes tend to be more insensitive than abdominal adipocytes, therefore, glyceride inability absorbed into adipocytes leading the insulin resistance more severe [13]. Obese adipocytes also down-regulated to secret adiponectin which is a reason leading to dysfunctional fasting glucose [28]. Both obesity and diabetes are defined as metabolism disorder/ dysfunction which caused by impaired metabolic pathology, the insulin resistance is coincident in both obesity and diabetes [29] . There are three primary sites caused by insulin resistance including adipose tissue, muscle tissue and hepatic tissue but the adipose tissues contributes significant role in term of development of insulin resistance symptom, obese adipocytes is on low-inflammation status have more in sensitivity than normal [13] People with obesity and diabetes share several mutual factors associate with life style and nutritional habits such as physical inactivity, consume processed foods which contain

much of sugar, salt and use alcohol. Research has been shown that management of obese status in diabetic patients through intensive lifestyle intervention reduce the complication of diabetes in cardiovascular events [30].

Diabetes type 2 vs. hypertension

Hypertension is considered metabolic syndrome which is sharing many common associated factors relating with diet and lifestyle such as inactivity, stress, over eating [31]. The diabetes incidence in hypertension people are nearly 2.5 times higher than those who have normal hypertension [32]. In pathology term, hypertension could be considered as situation of low-grade of inflammation which been observed increasing level of pro-inflammatory cytokines such as IL-17, MCP- 1, IL-6 and CD40L which are also increase in diabetic situation [33,34].

Diabetes type 2 vs. pregnancy

Diabetes mellitus occurs in pregnancy period called gestational diabetes mellitus (GDM) occurs when pregnant woman's pancreatic is not functioned properly, therefore, the level of insulin in bloodstream is not adequate enough to control blood glucose leading to situation of high blood glucose which never occur previously. The dysfunctional pancreatic might be the result of increasingly growth hormone and cortisol, lactogen during the pregnancy of women [35]. There are several risk factors associate with GDM such as macrosomia which means birth weight > 4000g, obesity in pregnant women.

Diabetes type 2 vs. genetic and associated factor of family

Genetic plays important role in progression of diabetes type 2 with approximately around 26-75% the possibility of diagnosed with diabetes type 2 [36]. The genetic factor of diabetes is ambiguous, but research has indicated several genes in charge of diabetes development such as TCF7L2, KNCJ11, CAPN10, PPARG but the mechanism of these gene interact to affect type 2 diabetes is unclear [36]. The family factor also contributes major level of risk factor of diabetes due to sharing the mutual risk behaviors of physical activity and diet together, 40% possibility of people having one in their parents could lead to diabetes, and if both of their parent are diabetic this possibility is 70% [37].

The In-Directed Factors of Diabetes

Physical activity will support the maintenance of blood glucose

The benefits of physical activity to people never been diagnosed with diabetes type 2 is unambiguous. Finish diabetes prevention study indicated that walking at least 2.5 hours a week could reduce the incidence of diabetes approximately 69% [38].

Physical activity also promotes of Improving of diabetes status with lifestyle therapy in youth with diabetes mellitus type 2 [39] and help to reduce of fasting glucose level in bloodstream indicate the important role of physical activity with some metabolic disorders such as diabetes mellitus type-2. There are several studies suggested that appropriate physical activity is protective factor of diabetes type-2 complications [40], the progression of diabetes type-2 reduced to 50% if applying the restricted diet and physical activity to diabetes type-2 [40] several researches has been indicated that exercise and nutrition diet help to improve the quality of life of patients with diabetes type 2 and improve the overall health.

Improving the quantities of physical activity to adequate amount of time and the diet modification has been proved having a significant impact in health of patients with pre-diabetes type-2 [41]. Research evidences show that the association of total body weight with the level of hyperglycemia and therefore, physical could contribute to improve the health status of patients with diabetes mellitus type -2 through reduce the total weight of body [42]. A systematic review of 12 clinical research has concluded that applying the modification of physical activity among people with diabetes contribute to delay the complications of diabetes [40], diabetes prevention program.

Physical activity will delay the development of diabetic complications

Physical activity in patient's activity consider are a preventive way to protect diabetic patients from complications and limit the progression of diabetes in general. WHO recommend that patients with diabetes in all types should have physical activity such as aerobi candwalking in order to improve health and reducing the possibility of complication. A systematic review of impact of physical activity and nutrition diet has been indicated that diet plays important role in treatment of diabetes type-2, patients recommended not to use much of glucose and lipid in order to prevent the complications of the diabetes.

Estimating the level of physical activity by metabolic equivalent (MET)

The level of physical activity among diabetic patients could be estimated by metabolic equivalent (MET) which means as the amount of oxygen consumed. One MET is equivalent to 3.5 ml O₂ per kilogram body weight x min [43].

Nutritional Diet

Vegetable

Nutritional diet has significant impact on diabetes process such as vegetarian. A study found that the level of fasting glucose significant reduced after 12 weeks of vegan diet [44]. Soy

consumption has been indicated has inversely association with diabetes [45] by increasingly expression gen of insulin receptor [46] and protein of soy also support the skeletal muscle mass in elderly diabetic patients, limit the consequence of reduction of muscle mass due to hyperglycemia, insulin resistance and endocrine changes [47] [14,15] Nutritional diet by that rich in fruit and vegetable is proved healthy for diabetes, protective factor of diabetes such as Mediterranean diet. This diet has been researched since 1960s which based on the food habits of population in the Mediterranean region [48]. One of the reasons this diet is healthy for diabetic patients because it contents diverse vegetables, fish [49], high level of adiponectin found in Greek adult population with Mediterranean diet [50], lower level of glucose, insulin and HOMA-IR [51].

Diabetes type 2 vs. beverage consumption

There are evidences illustrated that consumption of coffee, tea is preventive factor for diabetes in general population [52]. A systematic review from 12 studies has been concluded that consumption tea with more than 3 cup per day is preventive factor of diabetes mellitus type 2 [53] but the evidence is inconsistency through all of studies and it depends on the quality of tea has been consumed. Tea has many catechins including EGCG and other flavanols in green tea could support the function of pancreatic in term of secreting insulin, decreasing the levels of hyperglycemia and blood glucose [54]. Coffee is one of the most popular beverages in the world.

Coffee contains many substances could affect the health of consumer such as caffeine, cafestol & kahweol and some micronutrients [28]. Several protective cohort studies has concluded that consuming coffee decrease the incidence of diabetes type 2, consuming at least 7 cups of coffee per day could reduce the incidence of diabetes type 2 about 50% [55] but the association is dependent of the type of coffee consumption (boiled vs. filtered coffee) [56]. In Finland, people consume boiled coffee has been indicated as protective behavior [57] but in Demark, most Dutch people consumed filtered coffee and there is no association between coffee consumption and diabetes incidence [56] and the contamination included in coffee such as sugar and milk could have pathogenic effects [56]. Coffee consumption is inverse associated with diabetes development which are interpreting to reduce the level of insulin resistance in diabetic patients and decreasing level of pro-inflammatory such as IL-1, IL-6, TNF alpha and increasing level of anti-inflammatory such as adiponectin, IL-4, IL-10 [58,59]. The phenolic compounds in coffee can play important role in term of insulin-stimulated transferring glucose by activation GLUT4 and/or insulin receptor [60].

Sodium chloride and glucose consumption

One study concluded that in newly diagnosed diabetic

patients, eating much sodium chloride (NaCl) have 2-fold times higher of diagnosed diabetes compared to control group who take their salt consume in account [61]. Decreasing level of salt intake daily could increase the sensitive of insulin [62]. Diabetic patients need to control the amount of salt consumption in order to maintain the amount of water intake. The mechanism of too much salt consumption affect to diabetes might be though the promotion of inflammation reaction by unregulated of T-helper 17 and increasingly secret pro-inflammatory cytokines [63] which are similar mechanism of development of type 2 diabetes. Daily consumption of soft drink could increase 2 times of incidence of diabetes type 2 comparing with those who consumed less than 1 times per month [64].

Fat consumption

Fat consuming is main reason of obesity situation. Fatty acid from food will be stored in the adipocytes if over consuming and leading to overweight/ obesity.

Scientists has been confirmed that obese adipocytes increasingly secret many pro-inflammatory substance cause hypoglycemia and impaired glucose tolerance.

Alcohol consumption & smoking

Alcohol consumption and smoking are risk factors of diabetes though directly effect on pathology of diabetes and by development of obesity symptom which highly related to diabetes [65]. Alcohol consumption in diabetic patients could promote the development of the disease more serve due to promoting delay of modification of lifestyle [66], moderate alcohol has inversely association with diabetes progress in clinical research, but the result should be re-evaluated [65-67]. Heavy alcohol consumption is risk factor of diabetes due to dysfunction of glucose homeostasis in liver, therefore, leading to hypoglycemia [68]. Tobacco smoking is considered a risk factor of diabetes [69]. Tobacco contains mix of toxic which including 7000 chemicals. Tobacco smoking promoting the inflammation by increasingly secret Th2 cytokines pro-inflammatory substance leading to chronic inflammation [70] CDC reports that 30-40% smoking persons will likely develop diabetes type 2 [71] and smoking diabetic patients have more serious complications of diabetes such as heart and kidney disease, infection, eye diseases [72].

Mental Health

Mental health and psychology problem are associated factor of metabolism disease such as diabetes type 2 by promoting poor management of diet and physical activity such as over eating and inactivity or contribute to pathology of diabetes [73,74]. Through nervous system, the situation of mental health will be associated with the function of pancreatic therefore affect the level

of insulin secretion [75]. Mental health situation also promotes the status of inflammation more severely such as increasing level of IL-6, IL-1 beta and TNF, C-creative protein in schizophrenia, therefore, support the insulin insensitive more aggressively [76]. Diabetes mellitus type 2 occurs almost in elder people, cognitive performance of elder diabetic persons is lower than people without diabetes [77].

The Modification of Level of Physical Activity and Diet Habit and its Implication for Diabetes Progression

The benefit of physical activity and nutritional diet among pre-diabetic and risk group of diabetes has indicated in several study including cohort research [78-80] but the impacts of physical activity and nutritional diet on type 2 diabetic patients is not clear. The mechanism of impact of physical activity and nutritional diet to health of diabetic patients is changed since they were diagnosed with diabetes. Because diabetes type 2 is mainly caused by unhealthy of lifestyle, modifying lifestyle of diabetes type 2 mellitus patients required if patients diagnosed with the diabetes. In Australian, general practice management of diabetes patients recommend all patients should attend a structured education campaign after being diagnosed with diabetes, the curriculum including physical activity and nutritional diet modification [81] People with type 2 diabetes need to have adequate level of nutritional diet and physical activity to combat with development of diabetes and its complications.

Physical Activity on Health of Diabetic Patients

Studies has been suggested that people has been diagnosed with diabetes requires to have at least 30 minutes daily exercise [81,82]. Physical activity supports to reduce the insulin resistance and high level of glucose in blood stream by promoting the stream of glucose transfer to muscle [83], over weight and improve the function of pancreases [83].

| Factors | Increase/ reduce diabetes development | References |
|-----------------------|---|------------|
| Physical activity | Reduce | [40,84-86] |
| Alcohol consumption | Increase in heavy level Reduce in moderate level | [65,66,68] |
| Tobacco smoking | Increase | [70,72] |
| Fat consumption | Increase | [87-89] |
| Protein consumption | Reduce | [45,46] |
| Vegetable consumption | Reduce | [48,90,91] |
| Mental health | Increase | [75,77,92] |

Figure 1: Concluded picture of pathology of diabetes type 2.

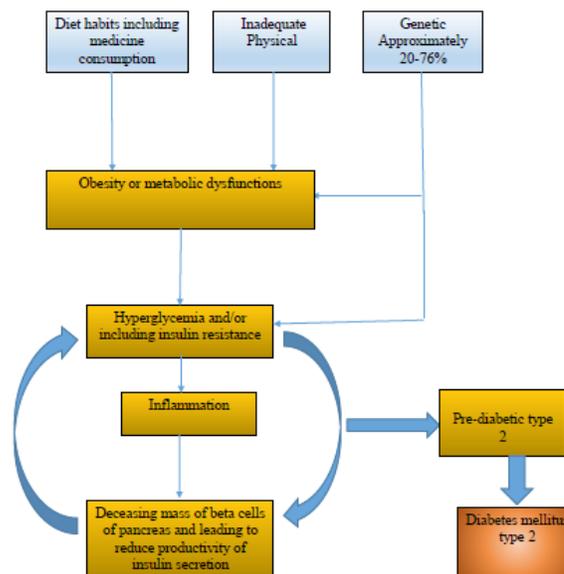


Figure 1: Concluded picture of pathology of diabetes type 2.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

- World health organisation (2016), GLOBAL REPORT ON DIABETES.
- Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, et al. (2010) Diabetes and Cancer: A consensus report. *Diabetes Care* 33: 1674-1685.
6. Obesity Management for the Treatment of Type 2 Diabetes (2016) *Diabetes Care* 39: S47-S51.
- Strasser B (2013) Physical activity in obesity and metabolic syndrome. *Annals of the New York Academy of Sciences* 1281: 141-159.
- Al-Goblan AS, Al-Alfi MA, Khan MZ (2014) Mechanism linking diabetes mellitus and obesity. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 7: 587-591.
- Chong S, Ding D, Byun R, Comino E, Bauman A, et al. (2017) Lifestyle Changes After a Diagnosis of Type 2 Diabetes. *Diabetes Spectrum: A Publication of the American Diabetes Association* 30: 43-50.
- Pahwa R, Jallal I (2018) Chronic Inflammation. [Updated 2018 Apr 19]. 2018 StatPearls Publishing: StatPearls [Internet]. TreasureIsland
- Roep BO (2003) The role of T-cells in the pathogenesis of Type 1 diabetes: from cause to cure. *Diabetologia* 46: 305-321.
- Krzewska A, Ben-Skowronek I (2016) Effect of Associated Autoimmune Diseases on Type 1 Diabetes Mellitus Incidence and Metabolic Control in Children and Adolescents. *BioMed Research International* 2016: 6219730.

10. Philippe MF, Benabadi S, Barbot-Trystram L, Vadrot D, Boitard C, et al (2011) Pancreatic volume and endocrine and exocrine functions in patients with diabetes. *Pancreas* 40: 359-363.
11. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, et al. (2003) Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 52: 102-110.
12. Kasuga M (2006) Insulin resistance and pancreatic β cell failure. *Journal of Clinical Investigation* 116: 1756-1760.
13. Freeman AM, Pennings N (2018) Insulin Resistance, in *StatPearls*. StatPearls Publishing LLC.: Treasure Island (FL).
14. Wang X, Hu Z, Hu J, Du J, Mitch WE (2006) Insulin resistance accelerates muscle protein degradation: Activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. *Endocrinology* 147: 4160-4168.
15. Umegaki H (2016) Sarcopenia and frailty in older patients with diabetes mellitus. *Geriatr Gerontol Int* 16: 293-299.
16. Bloomgarden ZT (2004) Consequences of Diabetes. *Diabetes Care* 27: 1825-1831.
17. Kologrivova IV, Suslova TE, Koshelskaya OA, Vinnizkaya IV, Popov SV (2016) T-helper-1, T-helper-17, T-regulatory lymphocytes in hypertensive patients with diabetes mellitus type 2 or impaired glucose tolerance: association with clinical and metabolic parameters in a case control study. *Translational Medicine Communications* 1: 2.
18. Wellen KE, Hotamisligil GS (2005) Inflammation, stress, and diabetes. *Journal of Clinical Investigation* 115: 1111-1119.
19. Bikman BT, Summers SA (2011) Ceramides as modulators of cellular and whole-body metabolism. *J Clin Invest* 121: 4222-4230.
20. Thagaard IN, Krebs L, Holm JC, Lange T, Larsen T, et al. (2017) Adiponectin and leptin as first trimester markers for gestational diabetes mellitus: a cohort study. *Clin Chem Lab Med* 55: 1805-1812.
21. Moller DE (2000) Potential role of TNF- α in the pathogenesis of insulin resistance and type 2 diabetes. *Trends Endocrinol Metab* 11: 212-217.
22. Cawthorn WP, Sethi JK (2008) TNF- α and adipocyte biology. *FEBS letters* 582: 117-131.
23. Stephens JM, Lee J, Pilch PF (1997) Tumor necrosis factor- α -induced insulin resistance in 3T3-L1 adipocytes is accompanied by a loss of insulin receptor substrate-1 and GLUT4 expression without a loss of insulin receptor-mediated signal transduction. *J Biol Chem* 272: 971-976.
24. Ruan H, Hacohen N, Golub TR, Van Parijs L, Lodish HF (2002) Tumor necrosis factor- α suppresses adipocyte-specific genes and activates expression of preadipocyte genes in 3T3-L1 adipocytes: nuclear factor- κ B activation by TNF- α is obligatory. *Diabetes* 51: 1319-1336.
25. Pollack RM, Donath MY, LeRoith D, Leibowitz G (2016) Anti-inflammatory Agents in the Treatment of Diabetes and Its Vascular Complications. *Diabetes Care* 39: S244-S252.
26. Baum JD, Ounsted M, Smith MA (1975) Weight gain in infancy and subsequent development of diabetes mellitus in childhood. *Lancet* 2: 866.
27. Harder T, Roepke K, Diller N, Stechling Y, Dudenhausen JW, et al. (2009) Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis. *Am J Epidemiol* 169: 1428-1436.
28. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y (2017) Obesity and inflammation: the linking mechanism and the complications. *Archives of Medical Science: AMS* 13: 851- 863.
29. Barnes AS (2011) The Epidemic of Obesity and Diabetes: Trends and Treatments. *Texas Heart Institute Journal* 38: 142-144.
30. Dutton GR, Lewis CE (2015) The Look AHEAD Trial: Implications for Lifestyle Intervention in Type 2 Diabetes Mellitus. *Prog Cardiovasc Dis* 58: 69-75.
31. Cheung BM, Li C (2012) Diabetes and Hypertension: Is There a Common Metabolic Pathway? *Current Atherosclerosis Reports* 14: 160-166.
32. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL (2000) Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *Atherosclerosis Risk in Communities Study*. *N Engl J Med* 342: 905-912.
33. Ruef J, Browatzki M, Pfeiffer CA, Schmidt J, Kranzhöfer R (2007) Angiotensin II promotes the inflammatory response to CD40 ligation via TRAF-2. *Vasc Med* 12: 23-27.
34. De Miguel C, Rudemiller NP, Abais JM, Mattson DL (2015) Inflammation and hypertension: new under standings and potential therapeutic targets. *Current hypertension reports* 17: 507-507.
35. Gilmartin ABH, Ural SH, Repke JT (2008) Gestational Diabetes Mellitus. *Reviews in Obstetrics and Gynaecology* 1: 129-134.
36. Lu Q, Frank BH, Gang H (2008) Genes, Environment, and Interaction- sin Prevention of Type 2 Diabetes: A Focus on Physical Activity and Lifestyle Changes. *Current Molecular Medicine* 8: 519-532.
37. Ali O (2013) Genetics of type 2 diabetes. *World Journal of Diabetes* 4: 114-123.
38. Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, et al. (2003) The Finnish Diabetes Prevention Study (DPS). Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 26: 3230-3236.
39. McGavock J, Dart A, Wicklow B (2015) Lifestyle therapy for the treatment of youth with type 2 diabetes. *Curr Diab Rep* 15: 568.
40. Hemmingsen B, Gimenez-Perez G, Mauricio D, Roqué I Figuls M, Metzendorf MI, et al. (2017) Diet, physical activity or both for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk of developing type 2 diabetes mellitus. *Cochrane Database Syst Rev* 12: Cd003054.
41. Liu WY, Lu DJ, Du XM, Sun JQ, Ge J, et al. (2014) Effect of aerobic exercise and low carbohydrate diet on pre-diabetic non-alcoholic fatty liver disease in postmenopausal women and middle-aged men-the role of gut microbiota composition: study protocol for the AELC randomized controlled trial. *BMC Public Health* 14: 48.
42. Yalamanchi SV, Stewart KJ, Ji N, Golden SH, Dobs A, et al. (2016) The relationship of fasting hyperglycemia to changes in fat and muscle mass after exercise training in type 2 diabetes. *Diabetes Res Clin Pract* 122: 154-161.

43. Jetté M, Sidney K, Blümchen G (1990) Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clinical Cardiology* 13: 555-565.
44. Jenkins DJ, Kendall CW, Marchie A, Jenkins AL, Augustin LS, et al. (2003) Type 2 diabetes and the vegetarian diet. *Am J Clin Nutr* 78: 610s-616s.
45. Li W, Ruan W, Peng Y, Wang D (2018) Soy and the risk of type 2 diabetes mellitus: A systematic review and meta-analysis of observational studies. *Diabetes Res Clin Pract* 137: 190-199.
46. Iritani N, Sugimoto T, Fukuda H, Komiya M, Ikeda H (1997) Dietary soybean protein increases insulin receptor gene expression in Wistar fatty rats when dietary polyunsaturated fatty acid level is low. *J Nutr* 127: 1077-1083.
47. Miki A, Hashimoto Y, Matsumoto S, Ushigome E, Fukuda T, et al. (2017) Protein Intake, Especially Vegetable Protein Intake, Is Associated with Higher Skeletal Muscle Mass in Elderly Patients with Type 2 Diabetes. *J Diabetes Res* 2017: 7985728.
48. Keys A (1995) Mediterranean diet and public health: personal reflections. *Am J Clin Nutr* 61: 1321s-1323s.
49. Esposito K, Maiorino MI, Di Palo C, Giugliano D (2009) Adherence to a Mediterranean diet and glycaemic control in Type 2 diabetes mellitus. *Diabet Med* 26: 900-907.
50. Mantzoros CS, Williams CJ, Manson JE, Meigs JB, Hu FB (2006) Adherence to the Mediterranean dietary pattern is positively associated with plasma adiponectin concentrations in diabetic women. *Am J Clin Nutr* 84: 328-335.
51. Panagiotakos DB, Tzima N, Pitsavos C, Chrysohou C, Zampelas A, et al. (2007) The association between adherence to the Mediterranean diet and fasting indices of glucose homeostasis: the ATTICA Study. *J Am Coll Nutr* 26: 32-38.
52. Nguyen CT, Lee AH, Pham NM, Do VV, Ngu ND, et al. (2018) Habitual tea drinking associated with a lower risk of type 2 diabetes in Vietnamese adults. *Asia Pac J Clin Nutr* 27: 701-706.
53. Jian Yang, Qun-Xia Mao, Hong-Xia Xu, Xu Ma, Chun-Yu Zeng (2014) Tea consumption and risk of type 2 diabetes mellitus: a systematic review and meta-analysis update. *BMJ Open* 4: e005632.
54. Martin MA, Goya L, Ramos S (2017) Protective effects of tea, red wine and cocoa in diabetes. Evidences from human studies. *Food Chem Toxicol* 109: 302-314.
55. van Dam RM, Feskens EJ (2002) Coffee consumption and risk of type 2 diabetes mellitus. *Lancet* 360: 1477-1478.
56. Reunanen A, Heliovaara M, Aho K (2003) Coffee consumption and risk of type 2 diabetes mellitus. *Lancet* 361: 702-3; author reply 703.
57. Carlsson S, Hammar N, Grill V, Kaprio J (2004) Coffee consumption and risk of type 2 diabetes in Finnish twins. *Int J Epidemiol* 33: 616-617.
58. Higdon JV, Frei B (2006) Coffee and health: a review of recent human research. *Crit Rev Food Sci Nutr* 46: 101-123.
59. Akash MS, Rehman K, Chen S (2014) Effects of coffee on type 2 diabetes mellitus. *Nutrition* 30: 755-763.
60. Tuomilehto J, Hu G, Bidel S, Lindström J, Jousilahti P (2004) Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. *Jama* 291: 1213-1219.
61. Radzeviciene L, Ostrauskas R (2017) Adding Salt to Meals as a Risk Factor of Type 2 Diabetes Mellitus: A Case-Control Study. *Nutrients* 9.
62. Fliser D, Nowack R, Allendorf-Ostwald N, Kohl B, Hübinger A, et al. (1993) Serum lipid changes on low salt diet. Effects of alpha 1- adrenergic blockade. *Am J Hypertens* 6: 320-324.
63. Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, et al. (2013) Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature* 496: 518-522.
64. Taylor LM, Johnson ST, Vallance JK, Staddy J, Basualdo-Hammond C (2014) Food and physical activity behaviours of adults attending a prediabetes education class. *Can J Diabetes* 38: 432-438.
65. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC (1995) Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 310: 555-559.
66. Alromaihi D, Zielke J, Bhan A (2012) Challenges of Type 2 Diabetes in Patients with Alcohol Dependence. *Clinical Diabetes* 30: 120-122.
67. Facchini F, Ida Chen YD, Reaven GM (1994) Light-to-Moderate Alcohol Intake Is Associated with Enhanced Insulin Sensitivity. *Diabetes Care* 17: 115-119.
68. Arky RA (1989) Hypoglycemia associated with liver disease and ethanol. *Endocrinol Metab Clin North Am* 18: 75-90.
69. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J (2012) Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *Jama* 298: 2654-2664.
70. Lee J, Taneja V, Vassallo R (2012) Cigarette Smoking and Inflammation: Cellular and Molecular Mechanisms. *Journal of Dental Research* 91: 142-149.
71. Smoking and Diabetes (2008) Centers for Disease Control and Prevention.
72. The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General (2014).
73. Balhara YPS (2011) Diabetes and psychiatric disorders. *Indian Journal of Endocrinology and Metabolism* 15: 274-283.
74. Robinson DJ, Luthra M, Vallis M (2013) Diabetes and Mental Health. *Canadian Journal of Diabetes* 37: S87-S92.
75. Mayr M, Schmid RM (2010) Pancreatic cancer and depression: myth and truth. *BMC Cancer* 10: 569-569.
76. Effendy E (2018) Exploring the link between inflammation and mental disorders. *IOP Conference Series: Earth and Environmental Science* 125: 012187.
77. Bangen KJ, Gu Y, Gross AL, Schneider BC, Skinner JC, et al. (2015) Relationship Between Type 2 Diabetes Mellitus and Cognitive Change in a Multiethnic Elderly Cohort. *J Am Geriatr Soc* 63: 1075-1083.
78. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, et al. (2015) Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. *Ann Intern Med* 163: 437-451.

79. Tran VD, Lee AH, Jancey J, James AP, Howat P, et al. (2016) Community-based physical activity and nutrition programme for adults with metabolic syndrome in Vietnam: study protocol for a cluster-randomised controlled trial. *BMJ Open* 6: e011532.
80. Pronk NP, Remington PL (2015) Combined Diet and Physical Activity Promotion Programs for Prevention of Diabetes: Community Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 163: 465-468.
81. Royal Australian College of General Practitioners, General practice management of type 2 diabetes 2014-15.
82. Briffa TG, Maiorana A, Sheerin NJ, Stubbs AG, Oldenburg BF, et al. (2006) Physical activity for people with cardiovascular disease: recommendations of the National Heart Foundation of Australia. *Med J Aust* 184: 71-75.
83. Bao Y, Michaud DS (2008) Physical activity and pancreatic cancer risk: a systematic review. *Cancer epidemiology, biomarkers & prevention* 17: 2671-2682.
84. The Diabetes Prevention Program Research Group (2002) The Diabetes Prevention Program (DPP): Description of lifestyle intervention. *Diabetes care* 25: 2165-2171.
85. Nguyen TH, Tang HK, Kelly P, van der Ploeg HP, Dibley MJ (2010) Association between physical activity and metabolic syndrome: a cross sectional survey in adolescents in Ho Chi Minh City, Vietnam. *BMC Public Health* 10: 141.
86. Kazaz İ, Angin E, Kabaran S, İyigün G, Kirmizigil B, et al. (2018) Evaluation of the physical activity level, nutrition quality, and depression in patients with metabolic syndrome: Comparativestudy. *Medicine (Baltimore)* 97: e0485.
87. Bergman RN, Ader M (2000) Free fatty acids and pathogenesis of type 2 diabetes mellitus. *Trends Endocrinol Metab* 11: 351-356.
88. Barnard ND, Scialli AR, Turner-McGrievy G, Lanou AJ, Glass J (2005) The effects of a low-fat, plant-based dietary intervention on body weight, metabolism, and insulin sensitivity. *Am J Med* 118: 991-997.
89. van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB (2002) Dietary fat and meat intake in relation to risk of type 2 diabetes in men. *Diabetes Care* 25: 417-424.
90. Esposito K, Giugliano D (2014) Mediterranean diet and type 2 diabetes. *Diabetes Metab Res Rev* 30: 34-40.
91. Esposito K, Maiorino MI, Ceriello A, Giugliano D (2010) Prevention and control of type 2 diabetes by Mediterranean diet: a systematic review. *Diabetes Res Clin Pract* 89: 97-102.
92. Ducat L, Philipson LH, Anderson BJ (2014) The Mental Health Comorbidities of Diabetes. *JAMA* 312: 691-692.