

A REVIEW: CONTROL OF DIABETES MELLITUS COMPLICATIONS**Abdul Wahid Ishaque*, Nishant Khatiwada and Kumar Khatiwada**

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ABSTRACT

Diabetes complications are wide ranging and due at least in part to chronic elevation of blood glucose levels, which leads to damage of blood vessels. According to international Diabetes Federation, about 415 million people are suffering from diabetes worldwide. This number is expected to exceed 640 million by the year 2040. The complications that are specific to diabetes include retinopathy, nephropathy, and neuropathy. Patients with all forms of diabetes of sufficient duration, including insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), are vulnerable to these complications, which cause serious morbidity. Adults with diabetes have an annual mortality of about 5.4% (double the rate for non-diabetic adults), and their life expectancy is decreased on average by 5-10 years. Although the increased death rate is mainly due to cardiovascular disease, deaths from non-cardiovascular causes are also increased. Cost of treatment has also been a burden on the patient living with diabetes and also for counties especially the developing ones. In conclusion, ensuring that blood glucose concentration is normal, regular checkup and cessation smoking can help control diabetes complications.

KEYWORDS: Hyperglycemia, Smoking, Glucose, Atherosclerosis.**INTRODUCTION**

Diabetes mellitus (DM) is described as a metabolic disorder characterized by hyperglycemia that occurs as a consequence of defects in insulin secretion, insulin action or both.^[1] These deficiencies lead to increase in the blood glucose concentrations which in turn damage many of the body's system such as blood vessels and nerves.^[2] According to international Diabetes Federation, about 415 million people are suffering from diabetes worldwide. This number is expected to exceed 640 million by the year 2040. In India, 69.2 million are living with diabetes and expected to cross 123.5 million by 2040.^[3] Complications of DM account for increased morbidity, disability, mortality and represent a threat for economies of all countries, especially the developing ones.^[4] It is estimated that half of patients with diabetes are unaware of their disease and thus more prone to developing diabetic complications.^[5] The aim of this review is to educate patients living with or unaware of their disease on the common complications and how to control or avoid it.

Complications of diabetes

Diabetes complications are wide ranging and due at least in part to chronic elevation of blood glucose levels, which leads to damage of blood vessels. **(Figure I).**

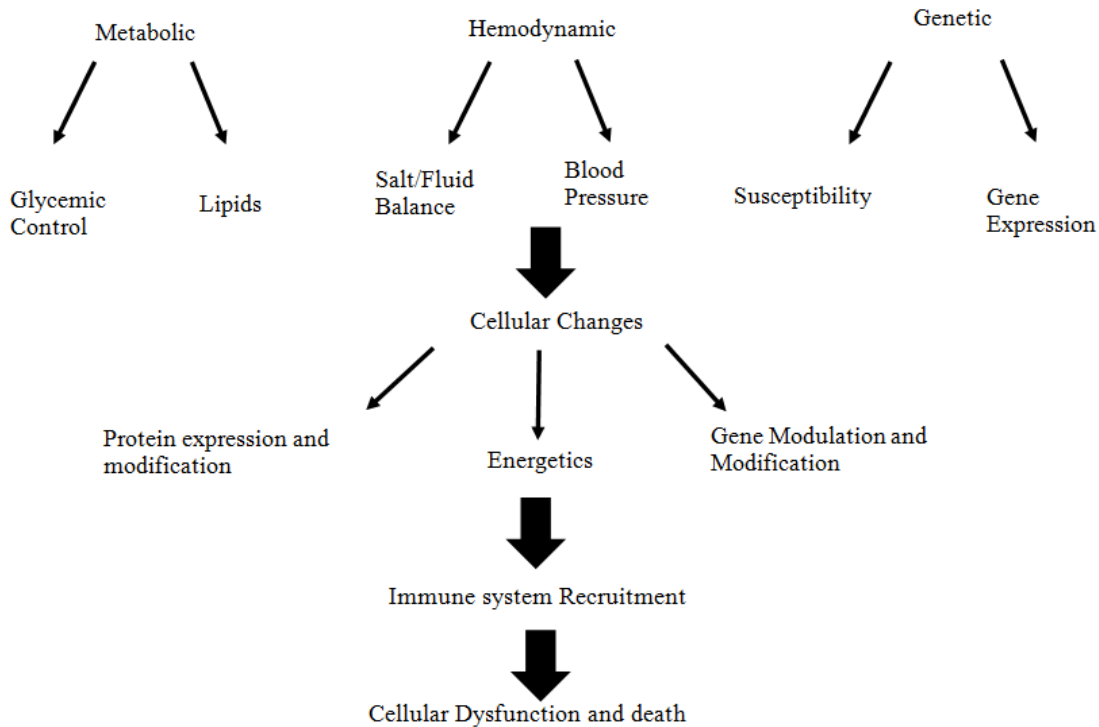


Fig I: Schematic overview of the major areas contributing to diabetic complications.

Complications of diabetes are results from poorly control of the concentration of blood sugar or may results from a person living with diabetes for more than 10 years. These complications can be distinguished into two forms (**Figure II**)

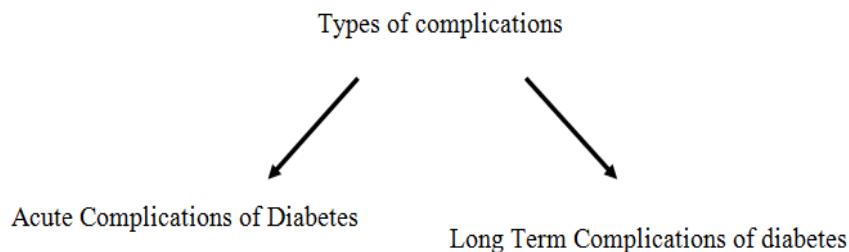


Fig II: Types of Diabetes Complication.

The acute complications can further divide into 3 major subdivisions which is related to short-term imbalance in blood sugar levels.

a) Hypoglycemia (abnormally low blood glucose): Hypoglycemia is defined by both the American Diabetes Association and European Association for the study of diabetes is when blood glucose level is $<70\text{mg/dl}$.^[6] Hypoglycemia is a condition characterized by an abnormally low level of blood glucose and has significant clinical consequences if left untreated. This complication may occur at any time of the day or night. It often occurs before meals, especially if meals are delayed or snacks are omitted. However, this level is neither an indication for treatment nor necessitates the presence of symptoms but may suggest a trend toward low sugars and warrant further explanation.^[7] Decrease in the blood glucose levels or its tissue utilization that

results in demonstrable signs or symptoms. Causes of hypoglycaemia are varied but in diabetic patients, it most often is iatrogenic. There are various important causes of hypoglycaemia are diabetic treatment changes, medication changes or overdoses, infections, dietary changes, changes in activity levels. There are other known causes like GI surgery, hepatic disease, starvation and others.^[8] In mild hypoglycaemia as the blood glucose level falls, the sympathetic nervous system is stimulated resulting in a surge of epinephrine and norepinephrine. This causes symptoms such as sweating, tremors, tachycardia, palpitation, nervousness, and hunger.^[9] Hypoglycaemia can also affect the central nervous system which leads to signs like inability to concentrate, headache, slurred speech, lightheadness, emotional changes.^[10] The CNS can be impaired to the extent that the diabetic patient may require assistance in navigating

such as disoriented behaviors, seizures, difficulty arousing from sleep or loss of consciousness.^[11]

Control: Diabetic patient experiencing hypoglycaemia should take in 15g of fast-acting concentrated source of carbohydrate such as 3 or 4 commercially prepared glucose tablets. The diabetic patient can also go for 4 to 6 oz of fruit juice or regular soda or 6 to 10 life savers or other hand candies and 2 to 3 teaspoons of sugar or honey. Unconscious patients can go for injection of glucagon 1mg subcutaneous or intramuscularly. **b)** Diabetic ketoacidosis (DKA) **c)** Hyperglycemia hyperosmolar non ketotic coma or hyperglycemia hyperosmolar syndrome (HHNS). Long-term complications happens when a person live longer with diabetes. The long-term complications are seen in both type 1 and type 2 diabetes but usually do not occur within 5 to 10 years of diagnosis.^[12] Diabetes complications can further be divided into 2 categories based on the blood vessels affected. **a)** Microvascular (due to damage to small blood vessels). **b)** Macrovascular (due to damage to larger blood vessels).^[13] Several landmark studies such as the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that strict glycemic control does limit microvascular while attempts to improve macrovascular outcomes through glucose-lowering interventions still remain shrouded with controversy.^[14]

Microvascular Complications

Patient with DM and associated Microvascular complications appear particularly at higher risk of accelerated atherosclerosis which ultimately culminates in cerebrovascular and cardiovascular events and premature death.^[15]

Diabetic Retinopathy

Diabetic retinopathy occurs due to the damage to the blood vessels of the retina in diabetic patients. This complication can be seen in either type 1 or type 2 diabetes as long as there is history of uncontrolled high blood sugar levels.^[16] Diabetic retinopathy are of 2 types **a)** Nonproliferative diabetic retinopathy (NPDR) also known as background retinopathy. Nonproliferative because the eyes do not make new blood vessels during the early stages of diabetic retinopathy. **b)** Proliferative diabetic retinopathy (PDR) also known as advanced retinopathy is the stage of retinopathy in which new blood vessels begin to grow within the retina. Diabetic retinopathy also recently was seen in approximately 10% of people with insulin resistance (prediabetes) and was associated with the presence of hypertension and a higher body mass index.^[17] Diabetic patient do not experience any symptoms until damage occurs inside the eye. Assuming symptoms do occur, the patient may experience floaters or dark spots, difficulty seeing at night, blurred vision, loss of vision and difficulty in distinguishing colors.^[18] The risk of developing diabetic retinopathy in diabetic patients have been found to be

related to both severities of hyperglycemia and presence of hypertension.^[19]

Control: Good metabolic control can delay the onset and progression of diabetic retinopathy. Regular checkup for any slight changes in vision is necessary to prevent future major damages and blindness.^[20] Control of hypertension, blood glucose concentration and cessation of smoking can help prevent diabetic retinopathy.^[21]

Diabetic Nephropathy

Diabetic nephropathy affects your kidney's ability to do their usual work of removing waste products and extra fluid from your body.^[22] It is defined by proteinuria > 500 mg in 24 hours in the setting of diabetes, but this is preceded by lower degrees of proteinuria, or "microalbuminuria." Microalbuminuria is defined as albumin excretion of 30-299 mg/24 hours.^[23] This complication involves both peripheral and autonomic nerves, affecting almost half of diabetic population.^[24] The first manifestation of DN is typically microalbuminuria, which progresses to overt albuminuria (i.e., increased albumin levels in the urine, indicating more severe renal dysfunction) and eventually to renal failure and is the leading cause of end-stage renal disease (ESRD).^[25]

Diabetic nephropathy may not show any early stages symptoms, but it only shows at the end stage like worsening blood pressure control, protein in urine, swelling of feet, ankles, hand eyes, increased need to urinate, reduced need for insulin or diabetes medicines. Patient at higher risks are those who smokes have high blood cholesterol, uncontrolled hypertension and high concentration of blood glucose.^[26]

Control: Evaluating autonomic nervous system function at the time of diagnosed and annually thereafter. Maintaining a healthy lifestyle and treating your diabetes and high blood pressure. Healthy weight and cessation of smoking have proven to prevent early diabetic nephropathy.^[27] At advanced stage patient may go for dialysis or kidney transplant.^[28]

Diabetic Neuropathy

A group of disease that affect all types of nerves including peripheral (sensorimotor), autonomic and special nerves.^[29] Diabetic neuropathy is regarded as the most common complication of diabetes which happens due to hyperglycemia and decreased blood flow to nerves by damaging small blood vessels.^[30] As with other microvascular complications, risk of developing diabetic neuropathy is proportional to both the magnitude and duration of hyperglycemia, and some individuals may possess genetic attributes that affect their predisposition to developing such complications.^[31]

These damages can lead to sensory loss, damage to limbs and impotence in diabetic men.^[32] The symptoms depend on which nerves affected for example, numbness in extremities, pain in extremities and impotence.

Decreased sensation to feet can lead to patient not recognizing cuts and developing foot infections (diabetic foot ulcer).^[33]

Control: Ensure that blood glucose concentration is normal or under control. Eat a balanced diet that includes a variety of healthy foods especially vegetables, fruits and grains.^[34] Regular exercise helps in lowering blood sugar, improve blood flow and keeps your heart healthy.^[35]

Macrovascular complications

Macrovascular complications result from changes in the medium to large blood vessels. These blood vessels wall thicken, sclerose and become occluded by plaque that adheres to the vessel walls which eventually block blood flow.^[36] Although the precise mechanism through which diabetes increase the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound.^[37,23]

Coronary artery disease

Coronary artery disease accounts for about 70% of death in people living with diabetes (type 2 diabetes) compared to people without diabetes who are controlling all the traditional risk factors for coronary artery disease such as age, obesity, tobacco use, dyslipidemia and hypertension.^[38] People living with diabetes have a 5-fold-greater risk for first myocardial infarction (MI) and a 2-fold-greater risk for a recurrent MI than people who had an MI but do not have diabetes.^[39] People living with diabetes (particularly type 2 diabetes) have many traditional risk factors for coronary artery disease which includes central obesity, dyslipidemia and hypertension.^[40]

Cerebrovascular disease

Diabetes is believed to be an independent risk factor across all ages for stroke. This risk is up to 2 to 4-fold greater in diabetic patients compared to non-diabetic patients which contributes to sudden and eventful death from stroke.^[41,35] As in Coronary artery disease, the presence of diabetes adversely affects the cerebrovascular circulation by increasing the risk of intracranial and extracranial atherosclerosis. People living with diabetes have an increased incidence of traditional risk factors for stroke such as hypertension, dyslipidemia, heart failure and atrial fibrillation.^[42] Hyperglycemia and hyperinsulinemia appear to be a significant factor for stroke.^[43]

Peripheral vascular disease

Peripheral vascular disease is characterized by occlusion of the lower-extremity arteries, this causes intermittent claudication and pain especially during exercise and activity which further leads to functional impairment and disability.^[44] It is believed that people living with diabetes are 15 times more likely to have lower-extremities amputation compared to non-diabetic people.^[45] Hyperglycemia is believed to be an

independent risk for peripheral vascular disease. In addition, hypertension, the use of tobacco, obesity, elevated serum fibrinogen levels and physical inactivity have also contributed to peripheral vascular disease.^[46]

Control of Macrovascular complications

Diabetic patient should ensure for regular checkup for the above-mentioned risk factors. Maintenance of healthy lifestyle and cessation of smoking can help prolong these complications.^[47,48]

CONCLUSION

Diabetes is associated with both microvascular and macrovascular diseases affecting numerous organs, including skeletal muscle, skin, heart, brain, kidneys and eyes. Common risk factors for vascular disease in diabetes include hyperglycemia, insulin resistance, dyslipidemia, hypertension, tobacco use, and obesity. The opportunities for effective physical therapy interventions (such as exercise), regular checkup, healthy lifestyle are significant.

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REFERENCE

1. Tripathi BK, Srivastava AK. Diabetes mellitus: complications and therapeutics. *Med Sci Monit*, Jul, 2006; 12(7): RA130-47.
2. Nagy A, Adany R, Sandor J. Effect of diagnosis-time and initial treatment on the onset of type 2 diabetes mellitus complications: a population-based representative cross-sectional study in Hungary. *Diabetes Res Clin Pract*, Dec, 2011; 94(3): e65-7.
3. Pradeepa R, Mohan V. Prevalence of type 2 diabetes and its complications in India and economic costs to the nation. *Eur J Clin Nutr.*, Jul, 2017; 71(7): 816-824.
4. Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. *Diabetes Care.*, May. 2020; 43(5): 964-974.
5. Tiptaradol S, Aekplakorn W. Prevalence, awareness, treatment and control of coexistence of diabetes and hypertension in thai population. *Int J Hypertens*, 2012; 2012: 386453.
6. Khunti K, Cigrovski Berković M, Ludvik B, Moberg E, Barner Lekdorf J, Gydesen H, Pedersen-Bjergaard U. Regional variations in definitions and rates of hypoglycaemia: findings from the global HAT observational study of 27 585 people with Type 1 and insulin-treated Type 2 diabetes mellitus. *Diabet Med.*, May 5, 2018; 35(9): 1232–41.

7. Marathe CS, Marathe JA, Rayner CK, Kar P, Jones KL, Horowitz M. Hypoglycaemia and gastric emptying. *Diabetes Obes Metab*, Mar, 2019; 21(3): 491-498.
8. Dissanayake HA, Keerthisena GSP, Gamage KKK, Liyanage JH, Ihalagama IRHS, Wijetunga WMUA, Tillekaratne TAD, Katulanda GW, Katulanda P. Hypoglycaemia in diabetes: do we think enough of the cause? An observational study on prevalence and causes of hypoglycaemia among patients with type 2 diabetes in an out-patient setting in Sri Lanka. *BMC Endocr Disord*, Jun 8, 2018; 18(1): 35.
9. Cryer PE. Hypoglycemia in diabetes: pathophysiological mechanisms and diurnal variation. *Prog Brain Res.*, 2006; 153: 361-5.
10. Rehni AK, Dave KR. Impact of Hypoglycemia on Brain Metabolism During Diabetes. *Mol Neurobiol*, Dec, 2018; 55(12): 9075-9088.
11. Tanaka Y, Takata T, Satomi T, Sakurai T, Yokono K. The double-edged effect of insulin on the neuronal cell death associated with hypoglycemia on the hippocampal slice culture. *Kobe J Med Sci.*, Jul 18, 2008; 54(2): E97-107.
12. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *J Pediatr*, Aug, 1994; 125(2): 177-88.
13. Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian J Endocrinol Metab*, Jul-Aug, 2016; 20(4): 546-51.
14. Terry T, Raravikar K, Chokrungravanon N, Reaven PD. Does aggressive glycemic control benefit macrovascular and microvascular disease in type 2 diabetes? Insights from ACCORD, ADVANCE, and VADT. *Curr Cardiol Rep.*, Feb, 2012; 14(1): 79-88.
15. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther.*, Nov, 2008; 88(11): 1322-35.
16. Prahs P, Helbig H. Augenerkrankungen bei Diabetes mellitus [Diabetic eye disease]. *Ther Umsch*, Mar, 2009; 66(3): 183-8.
17. Sun JK, Jampol LM. The Diabetic Retinopathy Clinical Research Network (DRCR.net) and Its Contributions to the Treatment of Diabetic Retinopathy. *Ophthalmic Res.*, 2019; 62(4): 225-230.
18. Heng LZ, Comyn O, Peto T, Tadros C, Ng E, Sivaprasad S, Hykin PG. Diabetic retinopathy: pathogenesis, clinical grading, management and future developments. *Diabet Med.*, Jun, 2013; 30(6): 640-50.
19. Moreno A, Lozano M, Salinas P. Diabetic retinopathy. *Nutr Hosp*, Mar, 2013; 28(2): 53-6.
20. Vujosevic S, Aldington SJ, Silva P, Hernández C, Scanlon P, Peto T, Simó R. Screening for diabetic retinopathy: new perspectives and challenges. *Lancet Diabetes Endocrinol*, Apr, 2020; 8(4): 337-347.
21. Shukla UV, Tripathy K. Diabetic Retinopathy. 2021 Feb 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021 Jan-.
22. Qi C, Mao X, Zhang Z, Wu H. Classification and Differential Diagnosis of Diabetic Nephropathy. *J Diabetes Res.*, 2017; 2017: 8637138.
23. Dyer AR, Greenland P, Elliott P, Daviglus ML, Claeys G, Kesteloot H, Ueshima H, Stamler J; INTERMAP Research Group. Evaluation of measures of urinary albumin excretion in epidemiologic studies. *Am J Epidemiol*, Dec 1, 2004; 160(11): 1122-31.
24. Jin HY, Lee KA, Park TS. The impact of glycemic variability on diabetic peripheral neuropathy. *Endocrine*, Sep, 2016; 53(3): 643-8.
25. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes Care*, Jan, 2005; 28(1): 164-76.
26. Umanath K, Lewis JB. Update on Diabetic Nephropathy: Core Curriculum 2018. *Am J Kidney Dis.*, Jun, 2018; 71(6): 884-895. doi: 10.1053/j.ajkd.2017.10.026. Epub 2018 Feb 3.
27. Nagib AM, Elsayed Matter Y, Gheith OA, Refaie AF, Othman NF, Al-Otaibi T. Diabetic Nephropathy Following Posttransplant Diabetes Mellitus. *Exp Clin Transplant*, Apr, 2019; 17(2): 138-146.
28. Girndt M. Diagnostik und Therapie der chronischen Nierenerkrankung [Diagnosis and treatment of chronic kidney disease]. *Internist (Berl)*, Mar, 2017; 58(3): 243-256.
29. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, Bril V, Russell JW, Viswanathan V. Diabetic neuropathy. *Nat Rev Dis Primers*, Jun 13, 2019; 5(1): 42.
30. Yagihashi S, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: Where are we now and where to go? *J Diabetes Investig*, Jan 24, 2011; 2(1): 18-32.
31. Winkler AS, Ejksjaer N, Edmonds M, Watkins PJ. Dissociated sensory loss in diabetic autonomic neuropathy. *Diabet Med.*, Jun, 2000; 17(6): 457-62.
32. Faselis C, Katsimardou A, Imprialos K, Deligkaris P, Kallistratos M, Dimitriadis K. Microvascular Complications of Type 2 Diabetes Mellitus. *Curr Vasc Pharmacol*, 2020; 18(2): 117-124.
33. Simoneau A, Foussard N, Blanco L, Domenge F, Monlun M, Poupon P, Rigalleau V. Mortality in patients with diabetic foot ulcer: Diabetic neuropathy is not innocent. A commentary on: "Amadou C et al. Five-year mortality in patients with diabetic foot ulcer during 2009-2010 was lower than expected. *Diabetes Metab*, 2019.
34. Obrosova IG, Ilnytska O, Lyzogubov VV, Pavlov IA, Mashtalir N, Nadler JL, Drel VR. High-fat diet induced neuropathy of pre-diabetes and obesity: effects of "healthy" diet and aldose reductase inhibition. *Diabetes*, Oct, 2007; 56(10): 2598-608.

35. Gu Y, Dennis SM, Kiernan MC, Harmer AR. Aerobic exercise training may improve nerve function in type 2 diabetes and pre-diabetes: A systematic review. *Diabetes Metab Res Rev.*, Feb, 2019; 35(2): e3099.
36. Viigimaa M, Sachinidis A, Toumpourleka M, Koutsampasopoulos K, Alliksoo S, Titma T. Macrovascular Complications of Type 2 Diabetes Mellitus. *Curr Vasc Pharmacol*, 2020; 18(2): 110-116.
37. Chistiakov DA, Sobenin IA, Orekhov AN, Bobryshev YV. Role of endoplasmic reticulum stress in atherosclerosis and diabetic macrovascular complications. *Biomed Res Int.*, 2014; 2014: 610140.
38. Sousa AG, Selvatici L, Krieger JE, Pereira AC. Association between genetics of diabetes, coronary artery disease, and macrovascular complications: exploring a common ground hypothesis. *Rev Diabet Stud.*, 2011; 8(2): 230-44.
39. Huang D, Refaat M, Mohammedi K, Jayyousi A, Al Suwaidi J, Abi Khalil C. Macrovascular Complications in Patients with Diabetes and Prediabetes. *Biomed Res Int.*, 2017; 2017: 7839101.
40. Fishman SL, Sonmez H, Basman C, Singh V, Poretsky L. The role of advanced glycation end-products in the development of coronary artery disease in patients with and without diabetes mellitus: a review. *Mol Med.*, Nov 23, 2018; 24(1): 59.
41. Chen R, Ovbiagele B, Feng W. Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. *Am J Med Sci.*, Apr, 2016; 351(4): 380-6.
42. Viigimaa M, Sachinidis A, Toumpourleka M, Koutsampasopoulos K, Alliksoo S, Titma T. Macrovascular Complications of Type 2 Diabetes Mellitus. *Curr Vasc Pharmacol*, 2020; 18(2): 110-116.
43. Magri CJ, Mintoff D, Camilleri L, Xuereb RG, Galea J, Fava S. Relationship of Hyperglycaemia, Hypoglycaemia, and Glucose Variability to Atherosclerotic Disease in Type 2 Diabetes. *J Diabetes Res.*, Jul 22, 2018; 2018: 7464320.
44. Asakawa H, Tokunaga K, Kawakami F. Comparison of risk factors of macrovascular complications. Peripheral vascular disease, cerebral vascular disease, and coronary heart disease in Japanese type 2 diabetes mellitus patients. *J Diabetes Complications*, Nov-Dec, 2000; 14(6): 307-13.
45. Mohammedi K, Woodward M, Hirakawa Y, Zoungas S, Colagiuri S, Hamet P, Harrap S, Poulter N, Matthews DR, Marre M, Chalmers J; ADVANCE Collaborative Group. Presentations of major peripheral arterial disease and risk of major outcomes in patients with type 2 diabetes: results from the ADVANCE-ON study. *Cardiovasc Diabetol*, Sep 2, 2016; 15(1): 129.
46. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther.*, Nov, 2008; 88(11): 1322-35.
47. Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, Karter AJ. The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study). *Diabetes Care*, Mar, 2019; 42(3): 416-426.
48. Pavlou DI, Paschou SA, Anagnostis P, Spartalis M, Spartalis E, Vryonidou A, Tentolouris N, Siasos G. Hypertension in patients with type 2 diabetes mellitus: Targets and management. *Maturitas*, Jun, 2018; 112: 71-77.