

EPIDEMIOLOGY OF PREDIABETES AND IT'S DIAGNOSIS AND TREATMENT: A REVIEW

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Abstract: A state of hyperglycemia known as prediabetes is characterized by glycemic indices that are above normal but still below the diabetes threshold. Pre-diabetes remains significantly connected with a yearly conversion rate of 5% to 10% to diabetes, even with differences in the diagnostic criteria among international professional organizations. Observational research suggests a potential link between prediabetes and diabetic sequelae, including small fiber neuropathy, early retinopathy, early nephropathy, and an increased risk of macrovascular disease. Numerous studies showing the value of lifestyle changes in avoiding diabetes have shown a relative risk reduction of 40%–70% in those with prediabetes. Although there is growing evidence that pharmaceutical therapy alternatives other than metformin are beneficial in preventing diabetes in individuals with prediabetes, their use is limited due to adverse effects. The health outcomes of childhood prediabetes have not been the subject of any rigorous evaluations. Pharmacotherapy for prediabetes may have uncertain consequences on a child's growth and pubertal development. High-risk individuals are advised to undergo secondary intervention with metformin pharmacotherapy; nevertheless, the eventual goal of therapy, the long-term cost-effectiveness of such interventions, and the advantages of early intervention are not well understood. In kids with prediabetes, pharmacotherapy needs to be used carefully. Prediabetes is the term for blood glucose levels that are higher than usual but not entirely above the diabetic threshold. In this at-risk status, diabetes is considered to be highly likely to develop. Even though prediabetes is usually an asymptomatic condition, it is always present before the beginning of diabetes. As hyperglycemia is a continuum, prediabetes cannot be ruled out as a completely benign illness. In this review, we discussed the difficulties in diagnosing prediabetes, the potential adverse health consequences that come with it, the available treatments for prediabetes, and the reasons behind using them.

Keywords: Lifestyle Modification, Prediabetes, Diabetes, Metformin, Impaired Glucose Tolerance

1. Epidemiology of Prediabetes

Prediabetes is becoming more widely identified as a significant metabolic condition. People with prediabetes are more likely to develop several pathologies typically related to diabetes, including diabetic retinopathy, neuropathy, nephropathy, and macrovascular complications. In addition, they are more likely to get diabetes in the future (Tabák et al., 2012). A cohort of participants in the Diabetes Prevention Program (DPP) who were at high risk of developing the condition had a 7.9% prevalence of diabetic retinopathy (Group, 2007). Peripheral neuropathy was more common in those with prediabetes than in people with appropriate glucose tolerance in a previous study (Lee et al., 2015), and it was similar to that of participants with recently diagnosed diabetes. The results of a meta-analysis have also revealed a connection between prediabetes and an increased risk of chronic kidney disease (CKD) (Echouffo-Tcheugui et al., 2016). Another meta-analysis (Huang et al., 2016) found that persons with prediabetes are more likely than those without the condition to experience cardiovascular disease, coronary heart disease, stroke, and all-cause death. Elevated plasma glucose levels indicative of prediabetes in early pregnancy are also associated with an increased risk of poor pregnancy outcomes and the possibility of gestational diabetes in a later pregnancy (Be, 2008).

Recently, codes that explicitly define "prediabetes" as a separate billable condition have been introduced to the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) (Chen et al., 2021). This provides more evidence that prediabetes is a different pathophysiological state from diabetes.

In 3-5 years, 25% of people with prediabetes may progress to overt type 2 diabetes (T2DM), and up to 70% of those with prediabetes will eventually acquire overt diabetes (Hostalek, 2019; Tabák et al., 2012). Chronic diabetes raises healthcare expenses significantly and has a detrimental long-term effect on quality of life (Saedi et al., 2019). However, prediabetes might be treated by using lifestyle modification plans that prioritize increasing physical activity and consuming a nutritious diet (Aschner, 2017; Association, 2019). If lifestyle modifications don't work, doctors may suggest medication like metformin or acarbose (Aschner, 2017; Association, 2019). One in three Americans have prediabetes, and 90% of them are ignorant of their illness, according to a commonly cited figure (Jackson et al., 2020). Still, how do these figures stack up to approximations from other studies conducted in other countries? This quick research assesses historical and contemporary trends in the global predominance of prediabetes.

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2. Diagnosis of Prediabetes

Several organizations have defined the definition of prediabetes. The World Health Organization (WHO) defines prediabetes as an intermediate hyperglycemia state based on two characteristics: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which are respectively defined as plasma glucose levels of 7.8–11.0 mmol/L (140–200 mg/dL) or 6.1–6.9 mmol/L (110–125 mg/dL) following the consumption of 75 g of oral glucose load, or a combination of the two based on a two-hour oral glucose tolerance test (OGTT) (Organization, 2006). On the other hand, prediabetes is defined by the American Diabetes Association (ADA) as having a HbA1c level between 5.7% and 6.4%. The ADA also has additional criteria depending on this level. The ADA has a lower cut-off value for IFG (100–125 mg/dL) but the same cut-off value for IGT (140–200 mg/dL) (Association, 2014a). Numerous studies have demonstrated poor associations between HbA1c, IFG, and IGT (Gosmanov and Wan, 2014). The usefulness of diagnosing diabetes or prediabetes based just on IFG and

IGT has been questioned due to the blood glucose cutpoints' inability to capture diabetes-related pathology and the probability of developing diabetes in the future (Guo et al., 2014). The validity of these cut-offs is further compromised by the low reproducibility of these tests in adults and adolescents (Genuth and Kahn, 2008; Van't Riet et al., 2010). Though it is well acknowledged that HbA1c represents an average blood sugar level—in principle, it should more accurately reflect hyperglycemia—this may not always hold. Despite valid concerns regarding the criteria, the diagnostic criteria for prediabetes still have a lower repeatability (approximately 50%) than that of diabetes (about 70%). Based on available data, prediabetes, as defined by various alternative criteria, appears to encompass an overlapping group of individuals with one or more anomalies in their glucose excursions. The incidence of both of these may indicate a more severe impairment in overall glucose homeostasis, and the occurrence of IFG and IGT likely identifies individuals with separate clinical abnormalities in their glucose metabolism.

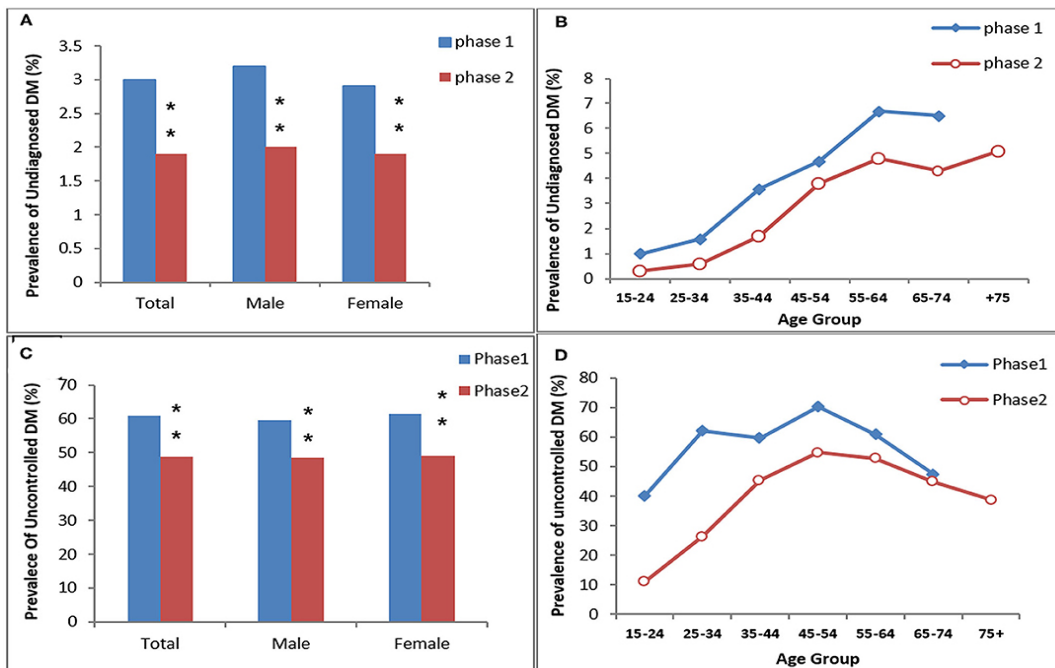


Fig 1: Prevalence and Incidence Rate of Diabetes, Pre-diabetes, Uncontrolled Diabetes in different age groups.

3. Prevalence of Prediabetes

Diabetes prevalence and mean FPG have been reported to be higher in both industrialized and developing nations (Cohen et al., 2006). The Centers for Disease Control and Prevention National Diabetes Statistics Report from 2009–2012 revealed that prediabetes impacted 37% of Americans over 20 and 51% of those over 65 based on fasting glucose or HbA1c readings (Barbagallo et al., 2011). These estimates suggest that approximately 86 million persons in the US alone had prediabetes in 2012. IGT was predicted to affect 343 million people (7.8%) globally in 2010; prevalence varied from 5.8% in Southeast Asia to 11.4% in North America and the Caribbean (Bansal, 2015). The International Diabetes Federation projects that 471 million individuals globally will have prediabetes by 2035.

4. Health Risks Associated with Prediabetes

Development of diabetes

The percentage of people who go from prediabetes to diabetes depends on both the characteristics of the population and the criteria used to diagnose prediabetes (Atlas, 2006; Forouhi et al., 2007). A 2007 meta-analysis evaluating the progression of prediabetes to diabetes [26] found that the annual incidence rate of diabetes was 4%–6% for isolated IGT, 6%–9% for isolated IFG, and 15%–19% for both IGT and IFG. Only research that was published before 2004 was included in this meta-analysis. Subsequently, significant studies showed similar annual incidence rates of the shift from prediabetes to diabetes. A Diabetes Prevention Program (DPP) Outcomes Study found that 11% of the control group was diabetic (Gerstein et al.,

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2007). In the US Multiethnic Study of Atherosclerosis, the IFG group had an annual incidence of diabetes of little over 4%.

The Toranomon Hospital Health Management Center Study found that the group with a HbA1c of 5.7%–6.4% had a 7% incidence of diabetes, while the IFG group had a 9% incidence (Yeboah et al., 2011). According to the results of the China Da Qing Diabetes Prevention Study (CDQDPS), the cumulative incidence of diabetes over 20 years was higher than 90% among patients with IGT, as assessed by repeated OGTT in the control group (Heianza et al., 2011). It has been shown that the definition of prediabetes using

ADA vs. WHO criteria affects the incidence rate of diabetes, with those defined by ADA criteria having a lower incidence than those defined by WHO criteria (Li et al., 2008). The possibility of developing diabetes can be predicted more accurately with continuous risk scores than with binary risk ratings, according to a panel of experts (EDEG et al., 2006). Studies have demonstrated that a diabetes risk score with a higher predictive value than IFG or IGT considers more readily available data, such as age, sex, ethnicity, systolic blood pressure, HDL cholesterol, fasting glucose, BMI, and family history of the illness (Bloomgarden, 2008).

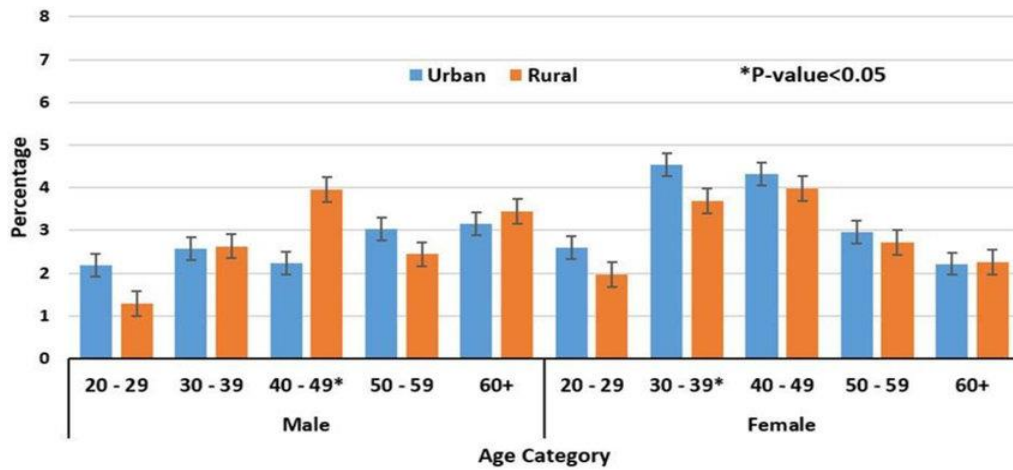


Fig 2: Prevalence of pre-diabetes in men and women according to age

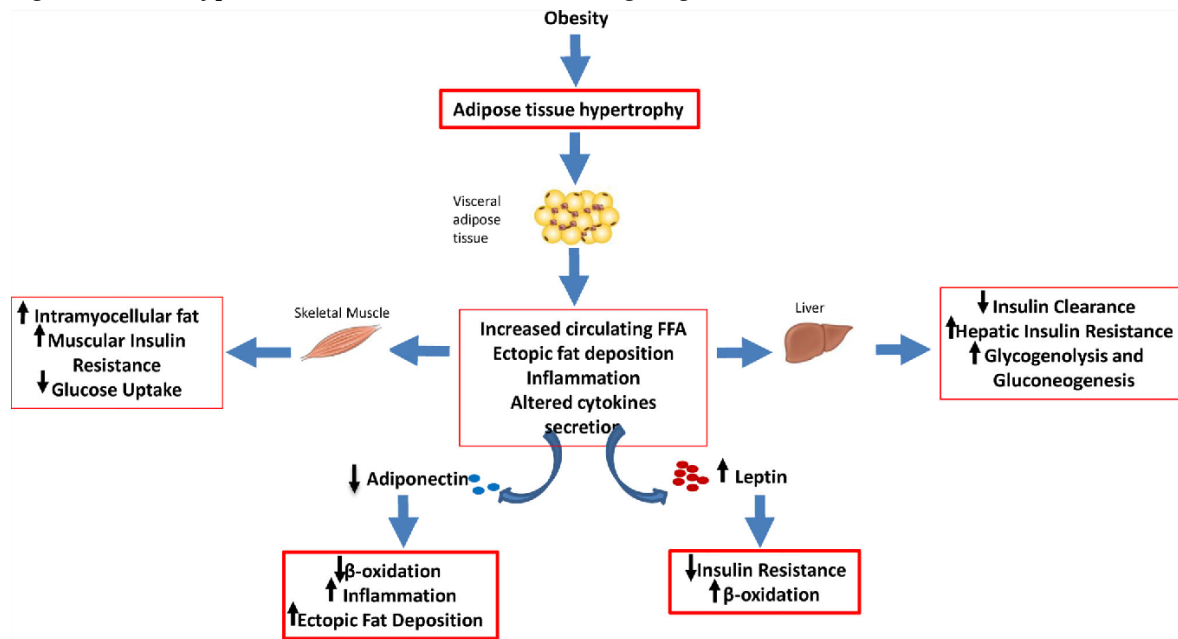


Fig 3: Mechanism of Action of Prediabetes

Renal diseases and neuropathy

A higher risk of early nephropathy and chronic renal illness has been associated with prediabetes in several studies (Gabir et al., 2000; Hoehner et al., 2002; Metcalf et al., 1993; Plantinga et al., 2010; Stern et al., 2002). We do not yet know why there is this correlation; it may be because the

population has a higher-than-normal prevalence of diabetes or that there are other factors besides prediabetes that are associated with hyperglycemia and nephropathy (Fox et al., 2005; Xu et al., 2009).

Neuro pathologies

Prediabetes is linked to dysfunction of the heart's autonomic nervous system, as evidenced by lower heart rate variability

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(Gerritsen et al., 2000; Schroeder et al., 2005; Singh et al., 2000; Tesfaye et al., 2010; Thomas et al., 2011), a decrease in the heart's parasympathetic modulation [45], and a higher incidence of erectile dysfunction in men with prediabetes (Wu et al., 2007). Non-invasive evaluation of neurological impairment in individuals with IGT has shown increased heat sensitivity thresholds, an increase in the prevalence of both hyperesthesia and hypoesthesia and significantly higher abnormalities in four out of five cardiovascular reflex tests (Grover et al., 2006). Increased rates of unpleasant sensory neuropathy, small fiber neuropathy, and idiopathic polyneuropathy have also been observed in studies on prediabetic individuals with IGT (Hoffman-Snyder et al., 2006; Singleton et al., 2001; Smith et al., 2001). According to the findings, little unmyelinated nerve fibers that regulate autonomic function, pain, and temperature may be involved in prediabetes, which precedes diabetes.

Retinopathy

Diabetic retinopathy was discovered to be present in over 8% of prediabetic research participants (Group, 2007). The results vary depending on the method of detection, even though several studies have connected prediabetes to an increased risk of diabetic retinopathy (Algvere et al., 1985; Nguyen et al., 2008; Nguyen et al., 2007; Stern et al., 2002; Tapp et al., 2008; Wong et al., 2002).

Cardiovascular disorders

Macrovascular disease has been linked to prediabetes, although it is unclear if this increased risk results from the development of prediabetes or the onset of diabetes (Collaboration, 2011; Sarwar et al., 2010). Cross-sectional studies have shown an increased incidence of coronary heart disease in individuals with prediabetes (Barr et al., 2007; Brunner et al., 2006). However, the relationship between prediabetes and coronary heart disease may be compounded by the common risk factors of these two illnesses.

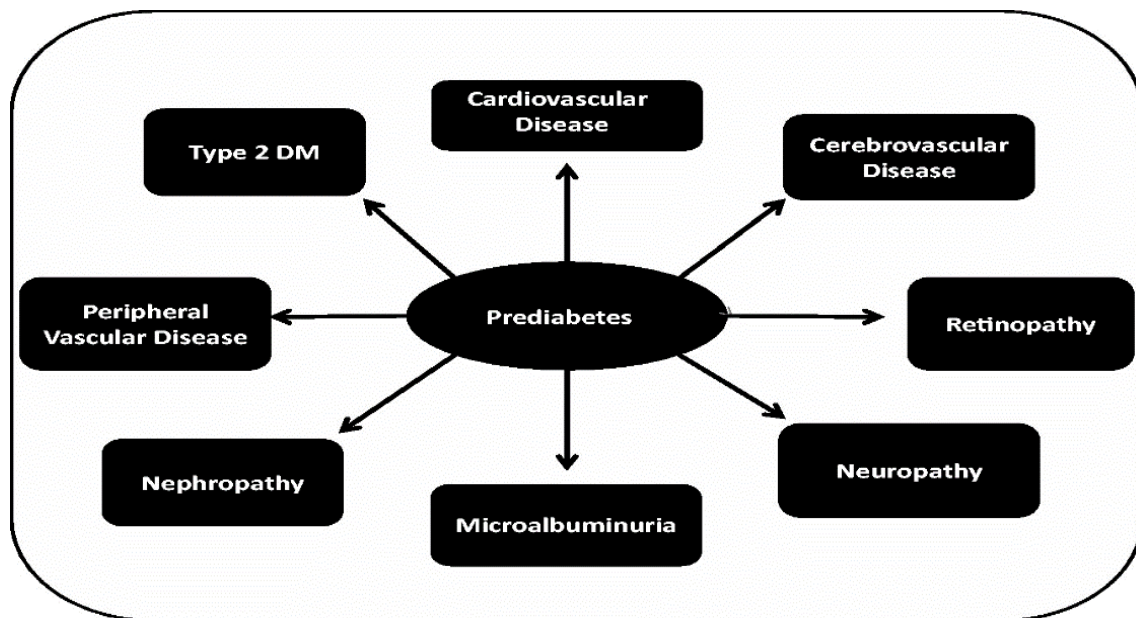


Fig 4: Health risks associated with prediabetes

5. Treatment for Prediabetes

Lifestyle modifications

The main objective of lifestyle intervention programs, which alter the modifiable risk factors of prediabetes and diabetes, is to target obesity with more significant physical activity and nutritional changes. The benefits of lifestyle changes have been shown by the two most extensive studies on diabetes prevention, the United States Diabetes Prevention Study (DPP) and the Finnish Diabetes Prevention Study (DPS) (Group, 2002; Tuomilehto et al., 2001). At the 3-year follow-up in the DPP trial, intensive lifestyle interventions (ILS) reduced risk by 58%. The goal of the ILS was to gain weight through food and exercise changes. Losing weight was found to be the main factor linked to a decrease in risk. This study found that for every kilogram a person lost in weight, their likelihood of developing diabetes decreased by 16% (Hamman et al., 2006). Benefits from the DPS were shown to be contingent on the participant meeting a certain number of pre-established intervention goals. These included losing more

than five percent of body weight, consuming less than thirty percent of energy from fat, less than ten percent from saturated fat, consuming more than or equal to fifteen grams of fiber per thousand calories, and engaging in more than four hours of activity each week (Tuomilehto et al., 2001). Even though most of the participants in both of these studies were Caucasians, research on Asian populations has also demonstrated similar effects (Ramachandran et al., 2006; Saito et al., 2011).

Drugs treatment

Research has been conducted on prediabetes in connection with several medication classes and treatments, such as biguanides, thiazolidinediones, α-glucosidase inhibitors, GLP-1 analogs, and non-antidiabetic medications and treatments such as bariatric surgery and anti-obesity pharmaceuticals. Metformin has long been used to treat diabetes, and research has shown that it can also have other beneficial effects, such as lowering body mass index (BMI) and improving cholesterol levels. A 45% decreased risk of

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developing type 2 diabetes is indicated by trial results from people with IGT (Lily and Godwin, 2009).

Metformin was found to be equally as beneficial as lifestyle intervention in the Indian DPP (IDPP) experiment. In contrast, it was less effective than lifestyle in the US DPP study (Group, 2002; Ramachandran et al., 2006). Metformin has been found to be more beneficial for people with higher BMI and FPG [64]. Several researchers have also studied metformin in obese children. Although statistically significant, the evidence suggests that lifestyle therapies can somewhat lower BMI, but the benefit is very transient—it peaks at six months. It vanishes at twelve months (McDonagh et al., 2014).

Artificial ligands called glitazones are made to attach to receptor- γ , which is activated by the peroxisome proliferator. Reduced gluconeogenesis in the liver and enhanced glucose absorption and utilization in the peripheral organs reduce insulin resistance (Smith, 2001). The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication was a three-year trial that demonstrated that rosiglitazone helped lower the incidence risk of diabetes by sixty percent. Significant side effects were also associated with it, though, such as an average weight gain of 2.2 kg in the intervention group compared to the control group and higher rates of heart failure (0.5% vs. 0.1%) and cardiovascular events (2.9% vs. 2.1%) overall (Investigators, 2008; Mohan, 2006). Pogliitazone was found to lower the risk of diabetes in obese individuals with IGT by more than 70% in the ACT NOW research. Alongside increases in carotid intima-media thickness rate, HDL cholesterol level, and diastolic blood pressure, there were also adverse effects, including increased weight gain (about 3 kg greater than placebo) and edema (13% vs. 6% in controls) (DeFronzo et al., 2011).

In the three-year prospective, double-blind, placebo-controlled IDPP-2 trial, there was no difference in the incidence of diabetes between participants receiving lifestyle intervention and placebo or between those receiving lifestyle intervention and pioglitazone. Modest doses of rosiglitazone and metformin were compared to placebo in the more recent Canadian Normoglycemia Outcomes Evaluation study to examine if the latter would lessen the incidence of type 2 diabetes while lowering the risk of adverse effects. Compared to 39% in the placebo group, 14% of patients in the active therapy group experienced incident diabetes. While the proportional risk reduction was 66% and the absolute risk reduction was 26%,

the individuals in the active therapy group reported more episodes of diarrhea (16% vs. 6% in the controls). Furthermore, 80% of the participants in the treatment group restored to normoglycemia, while only 53% of the subjects in the control group did so (Zinman et al., 2010). Because of safety concerns concerning weight gain, liver damage, increased cardiovascular risk, and a possible link to bladder cancer, the use of thiazolidinedione-related medicines for the treatment of prediabetes has generally been limited.

The postprandial rise in blood sugar is reduced by α -glucosidase inhibitors, such as acarbose and voglibose, which slow down the glucose absorption rate and extend the time it takes to digest carbohydrates overall (Bischoff, 1995). The STOP-NIDDM trial demonstrated that acarbose reduced the relative risk of diabetes by 25% in individuals with IGT over a 3.3-year follow-up. As a result of the medication's numerous gastrointestinal adverse effects, which included flatulence and diarrhea, 31% of study participants in the acarbose group discontinued before it was completed (Chiasson et al., 2002).

Suppressing glucagon and hepatic glucose production, slowing stomach emptying, decreasing appetite, and increasing postprandial insulin secretion are only a few physiological actions that GLP-1 analogs capitalize on (Tasyurek et al., 2014). In high-risk IGT patients taking voglibose over 48 weeks, a Japanese experiment discovered a 40% risk decrease in the occurrence of diabetes. Only 7% of participants stopped taking voglibose because of side effects, even though it was observed to have a comparable side effect profile to acarbose (Kawamori et al., 2009). Exenatide and liraglutide have been demonstrated to alleviate obesity in the long run and reduce the incidence of prediabetes in those who are obese for one to two years. Scholars have also investigated the connection between prediabetes and anti-obesity drugs such as Orlistat. The gastrointestinal lipase inhibitor orlistat reduces dietary fat absorption by about thirty percent when used as a weight-loss medication.

Research has shown that when Orlistat is used in conjunction with a low-energy diet, obese people lose more weight (6.7 kg vs. 3.8 kg) and experience a lower rate of conversion from IGT to overt diabetes (7.6% vs. 3.0%) over a 1.5-year follow-up period (Heymsfield et al., 2000). Orlistat's efficacy was further demonstrated by the XENDOS trial, which demonstrated a 37% relative risk reduction in the development of diabetes after four years of treatment (Torgerson et al., 2004).



Fig 5: Reversing prediabetes through lifestyle modification

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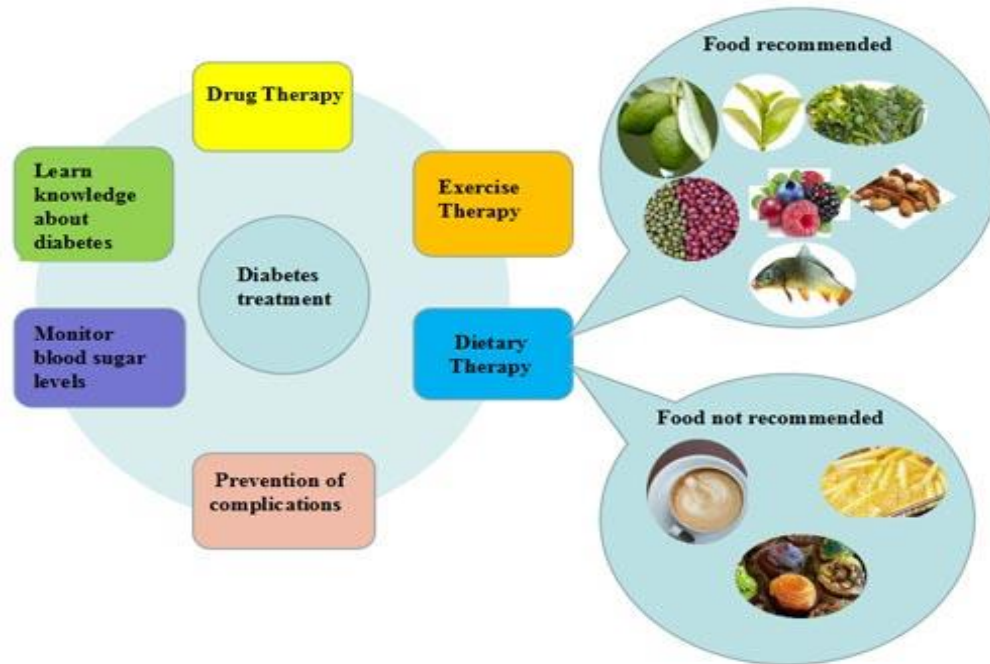


Fig 6: Treatment of Prediabetes

Bariatric procedures

In bariatric surgery, various procedures are performed to reduce caloric intake by creating a restrictive state, a malabsorptive state, or a combination of both. Among the procedures commonly done are sleeve gastrectomy, duodenal switch with biliopancreatic diversion, laparoscopic adjustable gastric banding, and Roux-en-Y gastric bypass. According to studies on Swedish obese subjects, bariatric surgery resulted in lasting weight loss (23.4% at 2 years and 16.1% at 10 years) and a 75% relative risk reduction of diabetes compared to controls (Sjöström et al., 2004). Furthermore, among individuals who were obese within two to ten years, bariatric surgery was associated with a lower prevalence of type 2 diabetes, cardiovascular disease, and cardiovascular death (Sjöström et al., 2004; Sjöström et al., 2012).

6. Benefits and Drawbacks of Diabetes Treatment

The fundamental hypotheses supporting prediabetes treatment include prevention of diabetes onset, diabetes consequences, and prevention of prediabetes consequences. Therapy aimed at treating prediabetes is effective in lowering the incidence of diabetes over time, as multiple studies have shown (Group, 2002; Heianza et al., 2011; Hopper et al., 2011; Natangelo et al., 1990). In the CDQDPS trial, which included a lifestyle intervention and a 20-year follow-up, the incidence of severe retinopathy was shown to be about 50% lower. On the other hand, there was no difference in the intervention and control groups' likelihood of acquiring additional microvascular problems, like nephropathy and neuropathy (Gong et al., 2011). There is occasionally variability in the evidence about the impact of interventions on macrovascular issues. A long-term lifestyle intervention program with an emphasis on physical activity and dietary counseling was found to reduce mortality among

IGT participants, even though this was not a randomized study (Eriksson and Lindgärde, 1998). Reducing the risk of stroke, lifestyle, and medication-based interventions for prediabetic subjects did not affect all-cause mortality, cardiovascular death, or myocardial infarction over a mean follow-up period of 3.8 years, according to a recent meta-analysis of all randomized control trials involving these subjects (Hopper et al., 2011). It is yet unclear what the long-term benefits will be in terms of microvascular or macrovascular repercussions, even if the currently available data indicates that several treatment techniques are beneficial in stopping the development of diabetes.

There is little evidence to support the idea that early intervention is preferable to late intervention, and there is a shortage of long-term research evaluating cost vs. benefit and long-term results associated with the ideal time to start glycemic intervention. The majority of published studies and guidelines concur that dietary modifications and increased physical activity should be the mainstays of lifestyle therapy for those with prediabetes to prevent diabetes. Health insurance companies often do not cover lifestyle interventions, even though they are a safe and effective way to avoid diabetes. The increasing effectiveness of pharmacotherapy lends credence to its use in treating prediabetes. Due to metformin's superior long-term safety profile and observed positive effects, organizations such as the ADA have recommended its use in some high-risk patients (Association, 2014b). However, the ultimate purpose of pharmacotherapy remains unclear. Very few children who have prediabetes have had a complete examination of prediabetes or its treatment. Research on the long-term impact of popular prediabetes medications on children's development during adolescence is lacking. Moreover, insulin resistance associated with puberty may overstate the overall incidence of diabetes in young people. The long-term efficacy and safety of

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treatment for children with prediabetes are not well-established.

Conclusion

In conclusion, there is still a need for a comprehensive evaluation of the health effects of prediabetes and any possible benefits of early intervention. It is essential to choose suitable research outcomes. In addition, the definition of prediabetes has to be revised to reflect the implications for long-term health more accurately. The time needed to fully comprehend the detrimental impacts of prediabetes and the rarity of some of these outcomes may limit the significance of this research despite their apparent importance. To create clinical guidelines for the treatment of prediabetes, there is not enough information available at this time. The management of prediabetes still heavily relies on lifestyle-related interventions. It is essential to employ pharmacotherapy on an individual basis.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned.

Consent for publication

Approved

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Not applicable

Conflict of interest

The authors declared absence of conflict of interest.

Author Contribution

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Conception of Study, Development of Research Methodology Design, Study Design., Review of manuscript, final approval of manuscript
Supervision, funding acquisition.

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ASAD SHABBIR

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MUHAMMAD AWAIS

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Supervision, funding acquisition.

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Data entry and Data analysis, drafting article.

References

- Algere, P., Efendić, S., Luft, R., and Wajngot, A. (1985). Retinal microangiopathy and pigment epithelial lesions in subjects with normal, borderline, and decreased oral glucose tolerance. *British journal of ophthalmology* **69**, 416-419.
- Aschner, P. (2017). New IDF clinical practice recommendations for managing type 2 diabetes in primary care. *Diabetes research and clinical practice* **132**, 169-170.
- Association, A. D. (2014a). Diagnosis and classification of diabetes mellitus. *Diabetes care* **37**, S81-S90.
- Association, A. D. (2014b). Standards of medical care in diabetes—2014. *Diabetes care* **37**, S14-S80.
- Association, A. D. (2019). 3. Prevention or delay of type 2 diabetes: standards of medical care in diabetes—2019. *Diabetes Care* **42**, S29-S33.
- Atlas, D. (2006). International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: International Diabetes Federation, 2015. *Eur. Respir. J* **27**, 188-207.
- Bansal, N. (2015). Prediabetes diagnosis and treatment: A review. *World journal of diabetes* **6**, 296.
- Barbagallo, C., Danaei, G., Finucane, M., Lu, Y., Singh, G., Cowan, M., Paciorek, C., Lin, J., Farzadfar, F., and Khang, Y. (2011). National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. *The Lancet* **378**, 31-40.
- Barr, E. L., Zimmet, P. Z., Welborn, T. A., Jolley, D., Magliano, D. J., Dunstan, D. W., Cameron, A. J., Dwyer, T., Taylor, H. R., and Tonkin, A. M. (2007). Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Circulation* **116**, 151-157.
- Be, M. (2008). Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* **358**, 1991-2002.
- Bischoff, H. (1995). The mechanism of alpha-glucosidase inhibition in the management of diabetes. *Clinical and investigative medicine. Medecine clinique et experimentale* **18**, 303-311.
- Bloomgarden, Z. T. (2008). American College Of Endocrinology pre-diabetes consensus conference: Part one. *Diabetes Care* **31**, 2062.
- Brunner, E. J., Shipley, M. J., Witte, D. R., Fuller, J. H., and Marmot, M. G. (2006). Relation between blood glucose and coronary mortality over 33 years in the Whitehall Study. *Diabetes care* **29**, 26-31.
- Chen, E. A., Roof, M. A., Lygrisse, K. A., Kurapatti, M., Hepinstall, M. S., and Schwarzkopf, R. (2021). ICD-10 coding mismatch in computer and robotic assisted primary total hip arthroplasty. *The Journal of Arthroplasty* **36**, 3934-3937.
- Chiasson, J.-L., Josse, R. G., Gomis, R., Hanefeld, M., Karasik, A., and Laakso, M. (2002). Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *The Lancet* **359**, 2072-2077.
- Cohen, R. M., Snieder, H., Lindsell, C. J., Beyan, H., Hawa, M. I., Blinko, S., Edwards, R., Spector, T. D., and Leslie, R. D. G. (2006). Evidence for independent heritability of the glycation gap (glycosylation gap) fraction of HbA1c in nondiabetic twins. *Diabetes care* **29**, 1739-1743.
- Collaboration, E. R. F. (2011). Diabetes mellitus, fasting glucose, and risk of cause-specific death. *New England Journal of Medicine* **364**, 829-841.
- DeFronzo, R. A., Tripathy, D., Schwenke, D. C., Banerji, M., Bray, G. A., Buchanan, T. A., Clement, S. C., Henry, R. R., Hodis, H. N., and Kitabchi, A. E. (2011). Pioglitazone

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- for diabetes prevention in impaired glucose tolerance. *New England Journal of Medicine* **364**, 1104-1115.
- Echouffo-Tcheugui, J., Narayan, K., Weisman, D., Golden, S. H., and Jaar, B. (2016). Association between prediabetes and risk of chronic kidney disease: a systematic review and meta-analysis. *Diabetic Medicine* **33**, 1615-1624.
- EDEG, Frouhi, N., Balkau, B., Borch-Johnsen, K., Dekker, J., Glumer, C., Qiao, Q., Spijkerman, A., Stolk, R., and Tabac, A. (2006). The threshold for diagnosing impaired fasting glucose: a position statement by the European Diabetes Epidemiology Group. *Diabetologia* **49**, 822-827.
- Eriksson, K.-F., and Lindgärde, F. (1998). No excess 12-year mortality in men with impaired glucose tolerance who participated in the Malmö Preventive Trial with diet and exercise. *Diabetologia* **41**, 1010-1016.
- Frouhi, N., Luan, J., Hennings, S., and Wareham, N. (2007). Incidence of type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990–2000. *Diabetic Medicine* **24**, 200-207.
- Fox, C. S., Larson, M. G., Leip, E. P., Meigs, J. B., Wilson, P. W., and Levy, D. (2005). Glycemic status and development of kidney disease: the Framingham Heart Study. *Diabetes care* **28**, 2436-2440.
- Gabir, M. M., Hanson, R. L., Dabelea, D., Imperatore, G., Roumain, J., Bennett, P. H., and Knowler, W. C. (2000). Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organization criteria for diagnosis of diabetes. *Diabetes care* **23**, 1113-1118.
- Genuth, S., and Kahn, R. (2008). A step backward-or is it forward? *Diabetes Care* **31**, 1093.
- Gerritsen, J., Dekker, J., TenVoorde, B., Bertelsmann, F., Kostense, P., Stehouwer, C., Heine, R., Nijpels, G., Heethaar, R., and Bouter, L. (2000). Glucose tolerance and other determinants of cardiovascular autonomic function: the Hoorn Study. *Diabetologia* **43**, 561-570.
- Gerstein, H. C., Santaguida, P., Raina, P., Morrison, K. M., Balion, C., Hunt, D., Yazdi, H., and Booker, L. (2007). Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. *Diabetes research and clinical practice* **78**, 305-312.
- Gong, Q., Gregg, E., Wang, J., An, Y., Zhang, P., Yang, W., Li, H., Li, H., Jiang, Y., and Shuai, Y. (2011). Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. *Diabetologia* **54**, 300-307.
- Gosmanov, A. R., and Wan, J. (2014). Low positive predictive value of hemoglobin A1c for diagnosis of prediabetes in clinical practice. *The American journal of the medical sciences* **348**, 191-194.
- Group, D. P. P. R. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England journal of medicine* **346**, 393-403.
- Group, D. P. P. R. (2007). The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabetic Medicine* **24**, 137-144.
- Grover, S. A., Lowensteyn, I., Kaouache, M., Marchand, S., Coupal, L., DeCarolis, E., Zoccoli, J., and Defoy, I. (2006). The prevalence of erectile dysfunction in the primary care setting: importance of risk factors for diabetes and vascular disease. *Archives of internal medicine* **166**, 213-219.
- Guo, F., Moellering, D. R., and Garvey, W. T. (2014). Use of HbA1c for diagnoses of diabetes and prediabetes: comparison with diagnoses based on fasting and 2-hr glucose values and effects of gender, race, and age. *Metabolic syndrome and related disorders* **12**, 258-268.
- Hamman, R. F., Wing, R. R., Edelstein, S. L., Lachin, J. M., Bray, G. A., Delahanty, L., Hoskin, M., Kriska, A. M., Mayer-Davis, E. J., and Pi-Sunyer, X. (2006). Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes care* **29**, 2102-2107.
- Heianza, Y., Hara, S., Arase, Y., Saito, K., Fujiwara, K., Tsuji, H., Kodama, S., Hsieh, S. D., Mori, Y., and Shimano, H. (2011). HbA1c 5.7–6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. *The Lancet* **378**, 147-155.
- Heymsfield, S. B., Segal, K. R., Hauptman, J., Lucas, C. P., Boldrin, M. N., Rissanen, A., Wilding, J. P., and Sjöström, L. (2000). Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Archives of Internal Medicine* **160**, 1321-1326.
- Hoehner, C. M., Greenlund, K. J., Rith-Najarian, S., Casper, M. L., and McClellan, W. M. (2002). Association of the insulin resistance syndrome and microalbuminuria among nondiabetic native Americans. The Inter-Tribal Heart Project. *Journal of the American Society of Nephrology* **13**, 1626-1634.
- Hoffman-Snyder, C., Smith, B. E., Ross, M. A., Hernandez, J., and Bosch, E. P. (2006). Value of the oral glucose tolerance test in the evaluation of chronic idiopathic axonal polyneuropathy. *Archives of neurology* **63**, 1075-1079.
- Hopper, I., Billah, B., Skiba, M., and Krum, H. (2011). Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: meta-analysis of randomised controlled clinical trials. *European Journal of Cardiovascular Prevention & Rehabilitation* **18**, 813-823.
- Hostalek, U. (2019). Global epidemiology of prediabetes-present and future perspectives. *Clinical diabetes and endocrinology* **5**, 5.
- Huang, Y., Cai, X., Mai, W., Li, M., and Hu, Y. (2016). Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *Bmj* **355**.
- Investigators, D. T. (2008). Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REDuction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes care* **31**, 1007-1014.
- Jackson, M. C., Dai, S., Skeete, R. A., Owens-Gary, M., Cannon, M. J., Smith, B. D., Jabrah, R., Masalovich, S. E., and Soler, R. E. (2020). An examination of gender differences in the National diabetes prevention program's lifestyle change program. *The Diabetes Educator* **46**, 580-586.
- Kawamori, R., Tajima, N., Iwamoto, Y., Kashiwagi, A., Shimamoto, K., and Kaku, K. (2009). Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *The lancet* **373**, 1607-1614.
- Lee, C. C., Perkins, B. A., Kayaniyl, S., Harris, S. B., Retnakaran, R., Gerstein, H. C., Zinman, B., and Hanley, A. J. (2015). Peripheral neuropathy and nerve dysfunction in individuals at high risk for type 2 diabetes: the PROMISE cohort. *Diabetes care* **38**, 793-800.
- Li, G., Zhang, P., Wang, J., Gregg, E. W., Yang, W., Gong, Q., Li, H., Li, H., Jiang, Y., and An, Y. (2008). The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *The Lancet* **371**, 1783-1789.

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- Lily, M., and Godwin, M. (2009). Treating prediabetes with metformin: systematic review and meta-analysis. *Canadian Family Physician* **55**, 363-369.
- McDonagh, M. S., Selph, S., Ozipinar, A., and Foley, C. (2014). Systematic review of the benefits and risks of metformin in treating obesity in children aged 18 years and younger. *JAMA pediatrics* **168**, 178-184.
- Metcalf, P. A., Baker, J. R., Scragg, R. K., Dryson, E., Scott, A. J., and Wild, C. J. (1993). Microalbuminuria in a middle-aged workforce: effect of hyperglycemia and ethnicity. *Diabetes Care* **16**, 1485-1493.
- Mohan, V. (2006). Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *The Lancet* **368**, 1096-1105.
- Natangelo, R., Luè, D., Bianchi, G., Ronchi, E., and Conti, D. (1990). The hypoglycemic reactions in diabetic patients in the emergency room. Which patients are going to be hospitalized? *Minerva Medica* **81**, 561-565.
- Nguyen, T. T., Wang, J. J., Islam, F. A., Mitchell, P., Tapp, R. J., Zimmet, P. Z., Simpson, R., Shaw, J., and Wong, T. Y. (2008). Retinal arteriolar narrowing predicts incidence of diabetes: the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study. *Diabetes* **57**, 536-539.
- Nguyen, T. T., Wang, J. J., and Wong, T. Y. (2007). Retinal vascular changes in pre-diabetes and prehypertension: new findings and their research and clinical implications. *Diabetes care* **30**, 2708-2715.
- Organization, W. H. (2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation.
- Plantinga, L. C., Crews, D. C., Coresh, J., Miller III, E. R., Saran, R., Yee, J., Hedgeman, E., Pavkov, M., Eberhardt, M. S., and Williams, D. E. (2010). Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. *Clinical journal of the American Society of Nephrology: CJASN* **5**, 673.
- Ramachandran, A., Snehalatha, C., Mary, S., Mukesh, B., Bhaskar, A., Vijay, V., and Programme, I. D. P. (2006). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* **49**, 289-297.
- Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., and Ogurtsova, K. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice* **157**, 107843.
- Saito, T., Watanabe, M., Nishida, J., Izumi, T., Omura, M., Takagi, T., Fukunaga, R., Bandai, Y., Tajima, N., and Nakamura, Y. (2011). Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. *Archives of internal medicine* **171**, 1352-1360.
- Sarwar, N., Gao, P., Seshasai, S., Gobin, R., Kaptoge, S., Di Angelantonio, E., Ingelsson, E., Lawlor Da, S. E., Stampfer, M., and Stehouwer CDa, L. S. (2010). Thompson a, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* **375**, 2215-22.
- Schroeder, E. B., Chambless, L. E., Liao, D., Prineas, R. J., Evans, G. W., Rosamond, W. D., and Heiss, G. (2005). Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes care* **28**, 668-674.
- Singh, J. P., Larson, M. G., O'Donnell, C. J., Wilson, P. F., Tsuji, H., Lloyd-Jones, D. M., and Levy, D. (2000). Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). *The American journal of cardiology* **86**, 309-312.
- Singleton, J. R., Smith, A. G., and Bromberg, M. B. (2001). Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes care* **24**, 1448-1453.
- Sjöström, L., Lindroos, A.-K., Peltonen, M., Torgerson, J., Bouchard, C., Carlsson, B., Dahlgren, S., Larsson, B., Narbro, K., and Sjöström, C. D. (2004). Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *New England Journal of Medicine* **351**, 2683-2693.
- Sjöström, L., Peltonen, M., Jacobson, P., Sjöström, C. D., Karason, K., Wedel, H., Ahlin, S., Anveden, Å., Bengtsson, C., and Bergmark, G. (2012). Bariatric surgery and long-term cardiovascular events. *Jama* **307**, 56-65.
- Smith, A. G., Ramachandran, P., Tripp, S., and Singleton, J. R. (2001). Epidermal nerve innervation in impaired glucose tolerance and diabetes-associated neuropathy. *Neurology* **57**, 1701-1704.
- Smith, U. (2001). Pioglitazone: mechanism of action. *International journal of clinical practice. Supplement*, 13-18.
- Stern, M. P., Williams, K., and Haffner, S. M. (2002). Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? *Annals of internal medicine* **136**, 575-581.
- Tabák, A. G., Herder, C., Rathmann, W., Brunner, E. J., and Kivimäki, M. (2012). Prediabetes: a high-risk state for diabetes development. *The Lancet* **379**, 2279-2290.
- Tapp, R. J., Tikellis, G., Wong, T. Y., Harper, C. A., Zimmet, P. Z., Shaw, J. E., Obesity, A. D., and Group, L. S. (2008). Longitudinal association of glucose metabolism with retinopathy: results from the Australian Diabetes Obesity and Lifestyle (AusDiab) study. *Diabetes care* **31**, 1349-1354.
- Tasyurek, H. M., Altunbas, H. A., Balci, M. K., and Sanlioglu, S. (2014). Incretins: their physiology and application in the treatment of diabetes mellitus. *Diabetes/metabolism research and reviews* **30**, 354-371.
- Tesfaye, S., Boulton, A. J., Dyck, P. J., Freeman, R., Horowitz, M., Kempler, P., Lauria, G., Malik, R. A., Spallone, V., and Vinik, A. (2010). Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes care* **33**, 2285-2293.
- Thomas, G., Sehgal, A. R., Kashyap, S. R., Srinivas, T. R., Kirwan, J. P., and Navaneethan, S. D. (2011). Metabolic syndrome and kidney disease: a systematic review and meta-analysis. *Clinical journal of the American Society of Nephrology: CJASN* **6**, 2364.
- Torgerson, J. S., Hauptman, J., Boldrin, M. N., and Sjöström, L. (2004). XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Clinical Diabetology* **5**, 95-104.
- Tuomilehto, J., Lindström, J., Eriksson, J. G., Valle, T. T., Hämäläinen, H., Ilanne-Parikka, P., Keinänen-Kiukaanniemi, S., Laakso, M., Louheranta, A., and Rastas, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine* **344**, 1343-1350.
- Van't Riet, E., Alssema, M., Rijkelijhuizen, J. M., Kostense, P. J., Nijpels, G., and Dekker, J. M. (2010). Relationship between A1C and glucose levels in the general Dutch population: the new Hoorn study. *Diabetes care* **33**, 61-66.

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- Wong, T. Y., Klein, R., Sharrett, A. R., Schmidt, M. I., Pankow, J. S., Couper, D. J., Klein, B. E., Hubbard, L. D., Duncan, B. B., and Investigators, A. (2002). Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. *Jama* **287**, 2528-2533.
- Wu, J.-S., Yang, Y.-C., Lin, T.-S., Huang, Y.-H., Chen, J.-J., Lu, F.-H., Wu, C.-H., and Chang, C.-J. (2007). Epidemiological evidence of altered cardiac autonomic function in subjects with impaired glucose tolerance but not isolated impaired fasting glucose. *The Journal of Clinical Endocrinology & Metabolism* **92**, 3885-3889.
- Xu, M., Li, X., Wang, J., Wang, X., Huang, Y., Cheng, Q., Huang, H., Li, R., Xiang, J., and Tan, J. (2009). Retinol-binding protein 4 is associated with impaired glucose regulation and microalbuminuria in a Chinese population. *Diabetologia* **52**, 1511-1519.
- Yeboah, J., Bertoni, A. G., Herrington, D. M., Post, W. S., and Burke, G. L. (2011). Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). *Journal of the American College of Cardiology* **58**, 140-146.
- Zinman, B., Harris, S. B., Neuman, J., Gerstein, H. C., Retnakaran, R. R., Raboud, J., Qi, Y., and Hanley, A. J. (2010). Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. *The Lancet* **376**, 103-111.



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