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Columns: REVIEW

Treatment of prediabetes

In this manuscript Kanat et al. review the literature regarding prediabetes pathophysiology and discuss how progression from prediabetes to type 2 diabetes can be prevented. The paper is well written and of interest for both clinicians and researchers. Major comments: 1. There is much focus on IGT and less on IFG in the paper, although both prediabetic states are included in the term prediabetes. More emphasis on IFG and prevention of progression from IFG to diabetes would strengthen the paper. There is currently not evidence for effective prevention in IFG with lifestyle or weight loss, but this fact is more or less ignored in the review and IFG/IGT is often combined in the conclusions although only studies in individuals with IGT are cited (e.g. page 8 and page 21). A statement about which strategy will be most beneficial for prevention of type 2 diabetes in individuals with IFG is lacking. Metformin is currently recommended for both IFG and IGT (mentioned on page 9) although no clear evidence exists regarding its usefulness in preventing progression to diabetes in IFG. This could also be discussed in more detail.

We agree with the reviewer about his comment regarding IFG and metformin. İn the original manuscript, we have extensively discussed the pathophysiology of IFG and its high risk of conversion to T2DM. However, because lack of stuides that have examined diabetes prevention , any discussion about the best strategy regarding the prevention of conversion of IFG to T2DM will be speculative. Nontheless, we have added the following discussion about the potential of metformin in the prevention of diabetes in IFG subjects: “Some small studies have demonstrated that metformin lowers the plasma glucose concentration in obese adolescence. However, no previous study has examined the efficacy of metformin in decresig the conversion rate of IFG to T2DM. Importantly, metformin was as effective as weight loss in decreasing the progression of IGT to T2DM in young (<65 years), obese (BMI>35) subjects and in subjects with fasting plasma glucose concentraiton >110 mg/dl (37). Thus, one would speculate that metformin would significantly lower the conversion rate from IFG to T2DM. A prospective randomized clinical trial is waranted for a definitive answer to this question.”

We also have added the following comment about the effect of lifestyle intervention on diabetes conversion in IFG subjects: “Although subjects with isolated IFG have similar risk to subjects with isolated IGT in conversion from IFG to T2DM, no major clinical trial has assessed the efficacy of lifestyle intervention in the prevention of conversion of IFG to T2DM.

A small study in Japanese subjects with IFG has reported that an intensive weight loss program was more effective in reducing the conversion rate from IFG to T2DM compared to less intensive intervention (HR=0.56, 95% CI=0.36-0.87). Subgroup analysis has revealed that subjects who had IFG+IGT at baseline manifested greater reduction in the conversion to T2DM (HR=0.41, 95% CI=0.24-0.69) while it was not statistically significant in subjects with isolated IFG (HR=1.17, 95% CI=0.50-2.74), and the difference in the lifestyle intervention on diabetes conversion between the two groups was statistically significant (p=0.03). "

Park MH, Kinra S, Ward KJ, White B, Viner RM Metformin for obesity in children and adolescents: a systematic review. Diabetes Care. 32:1743-5, 2009.

Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics. 107:E55, 2001

Atabek ME, Pirgon O Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo-controlled clinical trial. J Pediatr Endocrinol Metab. 21:339-48, 2008.

Saito T, Watanabe M, Nishida J, Izumi T, Omura M, Takagi T, Fukunaga R, Bandai Y, Tajima N, Nakamura Y, Ito M; Zensharen Study for Prevention of Lifestyle Diseases Group. Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med. 171:1352-60, 2011.

2. **HbA1c is now recommended for diagnosis of pre-diabetes and diabetes. Which implications do this have for the prevention of diabetes? The OGTT is seldom used in clinical practice and therefore IGT may not be detected. This issue should be addressed.**

We have added the following coment to the revised manuscript: "The ADA recently has suggested HbA1c=5.7-6.4% as a tool to identify subjects at high future diabetes risk. However, no previous study has utilized HbA1c as a screening tool to identify subjects at high risk (HbA1c =5.7-6.5%) and examined the efficacy of interventions to reduce the risk of conversion to T2DM. We and others previously have examined the concordance in high risk individuals identified with HbA1c versus OGTT and only little overlap between the two exists. Moreover, we also have shown that HbA1c was a poor predictors of impaired beta cell function which is the principle factor responsible for the converison of high risk individuals to overt diabetes. Thus, the following discussion will focus on diabetes prevention among high risk individuals identified based upon the OGTT, i.e. IFG/IGT."

Kanat M, Winnier D, Norton L, Arar N, Jenkinson C, Defronzo RA, Abdul-Ghani MA The relationship between {beta}-cell function and glycated hemoglobin: results from the veterans administration genetic epidemiology study. Diabetes Care. 34:1006-10, 2011

Færch, K, . Johansen NB, Witte DR, Lauritzen T, Jørgensen ME, Vistisen D. Relationship Between Insulin Resistance and β-Cell Dysfunction in Subphenotypes of Prediabetes and Type 2 Diabetes. JCEM 100: 707–716, 2015

Minor comments:

3. Page 5: First-phase insulin secretion is also impaired during IVGTT in IFG

We have added this information and the appropriate references to the revised manuscript and it now reads as follow: "IFG individuals have moderate hepatic insulin resistance and impaired early insulin response (0–30 min) during the OGTT and impaired fiirst phase insulin secretion measured with the hyperglycemic clamp and IVGTT"

Faerch K, Vaag A, Holst JJ, Glümer C, Pedersen O, Borch-Johnsen K Impaired fasting glycaemia vs impaired glucose tolerance: similar impairment of pancreatic alpha and beta cell function but differential roles of incretin hormones and insulin action. Diabetologia. 51:853-61, 2008

Kanat M, Mari A, Norton L, Winnier D, DeFronzo RA, Jenkinson C, Abdul-Ghani MA. Distinct β-cell defects in impaired fasting glucose and impaired glucose tolerance. 61:447-53, 2012

Meyer C, Pimenta W, Woerle HJ, Van Haeften T, Szoke E, Mitrakou A, Gerich J.Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans.Diabetes Care. 29:1909-14, 2006.

4. Page 5: Insulin resistance and beta cell function in IFG and IGT. See also

This reference has been added to the revised manuscript

Færch, K, . Johansen NB, Witte DR, Lauritzen T, Jørgensen ME, Vistisen D. Relationship Between Insulin Resistance and β-Cell Dysfunction in Subphenotypes of Prediabetes and Type 2 Diabetes. JCEM 100: 707–716, 2015

5. Page 6: Intervention to prevent the progression of IGT to T2DM. See also Saito et al. Arch Inter Med 2011.

We have added the above reference to the revised manuscript. Please see response to comment above

6. Page 6: Please add a reference to the following statement: "Weight loss, whether achieved via lifestyle modification, pharmacologic intervention or bariatric surgery, enhances insulin sensitivity, reduces the workload on the β-cells, and improves glucose tolerance in IGT individuals".

We have added the following references to this statment as requested

Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 54:2506-14, 2011

Muscelli E, Mingrone G, Camastra S, Manco M, Pereira JA, Pareja JC, Ferrannini E Differential effect of weight loss on insulin resistance in surgically treated obese patients. Am J Med. 118(1):51-7, 2005

Tiikkainen M, Bergholm R, Rissanen A, Aro A, Salminen I, Tamminen M, Teramo K, Yki-Järvinen H. Effects of equal weight loss with orlistat and placebo on body fat and serum fatty acid composition and insulin resistance in obese women.
Am J Clin Nutr. 79:22-30, 2004.

7. Page 11: Please add a reference to the following statement: "... although TZDs consistently have been at least twice as effective as metformin in reducing IGT conversion to T2DM".

We have added the following references to this statment as requested

Knowler WC, Hamman RF, Edelstein SL, Barrett-Connor E, Ehrmann DA, Walker EA, Fowler SE, Nathan DM, Kahn SE; Diabetes Prevention Program Research Group.
Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. Diabetes. 54:1150-6, 2005.

Merlotti C, Morabito A, Pontiroli AE. Prevention of type 2 diabetes; a systematic review and meta-analysis of different intervention strategies. Diabetes Obes Metab. 16:719-27, 2014.

8. Page 12: Please add a reference to the following statement: "GIP secretion is normal or slightly increased".

We have added the following reference to this statment as requested

Jones IR, Owens DR, Luzio S, Williams S, Hayes TM. The glucose dependent insulinotropic polypeptide response to oral glucose and mixed meals is increased in patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia. 32:668-77, 1989.

Answer to chief editor: Had correct the errors in the paper.