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Hidden Risks behind Normal Fasting Glucose: Is It Significant?

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Diabetes is diagnosed based on plasma glucose criteria—either fasting plasma glucose or 2-hour glucose value during a 75 g oral glucose tolerance test—or glycosylated hemoglobin (HbA1c) criteria [1]. Although it is generally known that these parameters are equally appropriate for diagnosis, most screening tests only measure fasting glucose levels due to cost-effectiveness and simplicity. This occasionally leads to misdiagnosis of diabetes in early stage.

In the article entitled "Predictors of incident type 2 diabetes mellitus in Japanese Americans with normal fasting glucose level," Hwang et al. [2] analyzed the incidence and predictors of diabetes development in a cohort of 370 Japanese Americans followed for ten years. This study enlightens us with two clinically important messages. First, only a small proportion (approximately 13%) of subjects with incident diabetes was diagnosed based on fasting plasma glucose criterion. Furthermore, 39.6% of subjects with incident diabetes during 10 years of follow-up had normal fasting glucose level at the time of diagnosis, suggesting that screening or diagnosis of diabetes relying on fasting plasma glucose might result in significant underdiagnoses. Many studies investigated the relative contribution of impaired beta-cell function or increased insulin resistance in the progression of fasting hyperglycemia or postprandial hyperglycemia, but controversy exists. Some Japanese studies demonstrated that deterioration of basal and early-phase insulin secretion, rather than insulin sensitivity, are mainly responsible for the development of impaired glucose tolerance and isolated post-challenge hyperglycemia [3,4]. Considering that Asians are more likely to have lower beta-cell mass and insulin secretory capacity compared to Caucasians [5], judgement based solely on fasting glucose levels might lead to a high probability of missing incident diabetes.

Second, higher fasting glucose level, although in normal range, was independently associated with increased risk of long-term diabetes development. This is generally consistent with previous studies demonstrating that there is a graded relationship between glucose levels in normal range and the risk of future diabetes [6-9]. These studies revealed that there is approximately 2- to 3-fold difference in risk within normal glucose range even after adjusting possible confounding factors. In a study examining the longitudinal trajectories of fasting plasma glucose levels and HbA1c, there was a larger increment in both parameters from 3 years to 1 year before diagnosis [10]. In the year before diagnosis, sudden increase in fasting plasma glucose and HbA1c occurred in incident cases. Importantly, the slope for fasting plasma glucose differed significantly during the 10 years of prediagnosis period between cases and noncases. Collectively, these data suggest that both the absolute value and the slope of fasting plasma glucose levels should be carefully monitored for the prevention of diabetes even if it is within the normal range. In addition, subjects with high normal-range fasting glucose levels (95 to 99 mg/dL) had 53% higher risk of developing cardiovascular diseases compared with subjects with low normal-range fasting glucose levels (<80 mg/dL) [11]. The distinct pattern of trajectories of long-term normal-range fasting glucose was also associated

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with the development of coronary heart disease [12]. These evidences indicate that high normal-range fasting glucose might not be a benign condition and needs special consideration.

In conjunction with other risk factors and biomarkers, further stratification of risk of diabetes in subjects within normal-range fasting glucose would aid in earlier diagnosis and establishing better preventive measures. Although it seems to be premature to consider lowering the cut-off of normal fasting glucose level, we still should keep our eye on the 'normal' glucose level.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. Diabetes Care 2018;41(Suppl 1):S13-27.
2. Hwang YC, Fujimoto WY, Kahn SE, Leonetti DL, Boyko EJ. Predictors of incident type 2 diabetes mellitus in Japanese Americans with normal fasting glucose level. Diabetes Metab J 2018;42:198-206.
3. Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. Diabetes Res Clin Pract 2004;66 Suppl 1:S37-43.
4. Mitsui R, Fukushima M, Nishi Y, Ueda N, Suzuki H, Taniguchi A, Nakai Y, Kawakita T, Kurose T, Yamada Y, Inagaki N, Seino Y. Factors responsible for deteriorating glucose tolerance in newly diagnosed type 2 diabetes in Japanese men. Metabolism 2006;55:53-8.
5. Cho JH, Kim JW, Shin JA, Shin J, Yoon KH. β-Cell mass in people with type 2 diabetes. J Diabetes Investig 2011;2:6-17.
6. Hayashino Y, Fukuhara S, Suzukamo Y, Okamura T, Tanaka T, Ueshima H. Normal fasting plasma glucose levels and type 2 diabetes: the high-risk and population strategy for occupational health promotion (HIPOP-OHP) [corrected] study. Acta Diabetol 2007;44:164-6.
7. Nichols GA, Hillier TA, Brown JB. Normal fasting plasma glucose and risk of type 2 diabetes diagnosis. Am J Med 2008;121:519-24.
8. Brambilla P, La Valle E, Falbo R, Limonta G, Signorini S, Cappellini F, Mocarelli P. Normal fasting plasma glucose and risk of type 2 diabetes. Diabetes Care 2011;34:1372-4.
9. Tirosh A, Shai I, Tekes-Manova D, Israeli E, Pereg D, Shochat T, Kochba I, Rudich A; Israeli Diabetes Research Group. Normal fasting plasma glucose levels and type 2 diabetes in young men. N Engl J Med 2005;353:1454-62.
10. Heianza Y, Arase Y, Fujihara K, Hsieh SD, Saito K, Tsuji H, Kodama S, Yahagi N, Shimano H, Yamada N, Hara S, Sone H. Longitudinal trajectories of HbA1c and fasting plasma glucose levels during the development of type 2 diabetes: the Toranomon Hospital Health Management Center Study 7 (TOPICS 7). Diabetes Care 2012;35:1050-2.
11. Shaye K, Amir T, Shlomo S, Yechezkel S. Fasting glucose levels within the high normal range predict cardiovascular outcome. Am Heart J 2012;164:111-6.
12. Yuan Z, Yang Y, Wang C, Liu J, Sun X, Liu Y, Li S, Xue F. Trajectories of long-term normal fasting plasma glucose and risk of coronary heart disease: a prospective cohort study. J Am Heart Assoc 2018;7:e007607.