Review Article

One-hour Post load Hyperglycemia : A Powerful but Underestimated Marker of Incident Diabetes and Related Complications

Gautam Jesrani[1], Monica Gupta[2], Samiksha Gupta[3], Saurabh Gaba[3]

Purpose of Review : Type 2 Diabetes and related complications, due to Hyperglycemia, are increasing in number Worldwide. Early identification of subclinical disease in the form of hyperglycemia can offer early intervention and delay the progression of irreversible micro and macro-vascular complications. The aim of this review article is to narrate the usefulness of One-hour post load Hyperglycemia in terms of prompt identification and timely management of glucose dysregulation.

Recent Findings : Literature has described that Hyperglycemia itself is an independent factor which can produce various complications, similar to Diabetes. Studies have shown that glycated haemoglobin is less superior in recognizing early Hyperglycemia and can miss a transient rise in blood glucose which subsequently gives rise to reactive oxygen species. This oxidative stress generates endothelial damage and dysfunction. Raised blood glucose levels form advanced glycation end products and generates sub-clinical inflammation, which cause pathological alteration in the vessel wall and increased process of Atherosclerosis. Fatty liver formation and progression to non-alcoholic Steatohepatitis is enhanced due to chronic relative insulin deficiency, reflected by post load Hyperglycemia. One-hour Hyperglycemia can identify β-cell dysfunction at an early stage. Recently, 30-minute plasma glucose value measurement was found to be successful in predicting overt Diabetes in limited trials.

[*J Indian Med Assoc* 2023; **121(6):** 51-6]

***Key words* : One-hour Post load Hyperglycemia, Glucose Tolerance Test, Insulin Resistance, Diabetes Related Complications.**

Pre-diabetes or intermediate hyperglycemia is an increment of Plasma Glucose (PG) levels exceeding the normal range which is less than the diagnostic cut-off for Diabetes. This deviation is usually missed with the current diagnostic markers and may lead to future diabetes and various irreversible complications. Diabetes mellitus and pre-diabetic dysglycemia / hyperglycemic abnormalities are increasing worldwide, owing to the rapid rise in obesity in both adults and adolescents. Around 366 million people in the world will be affected with diabetes by 2030[1]. The magnitude of this burden of Diabetes and pre-diabetes needs timely intervention to flatten the rising disease curve.

Elevated glucose levels to glucose load or impaired glucose tolerance starts with insulin resistance or decreased response to insulin by peripheral tissues, which occur due to Hyperglycemia itself, inflammation and obesity[2]. Individuals with Hyperglycemia or deranged PG tolerance are at danger for the evolution of overt Type 2 Diabetes Mellitus (T2DM) and related complications later in the future, and clinical studies have described that both lifestyle changes and appropriate timely pharmacological interventions prevent the advancement from impaired glucose tolerance to T2DM[3].

Editor's Comment :

- One-hour Post-load hyperglycemia is a superior marker in identifying glucose dysregulation and related complications at an earlier stage and can provide an important time frame, in which, intervention can delay or halt the progression of disease. It gives an advantage to recognize individuals at risk of growing related complication, when other markers are within normal range.

It is well-known that the β-cell numbers are reduced to 40% when an individual develops impaired fasting glucose[4]. Hyperglycemia to glucose loading and insulin resistance worsen over time, causing a continuous reduction in β-cell function that expands the chances of developing Type 2 Diabetes. In epidemiological studies, it is demonstrated that about 40% of those who develop T2DM in the future, had normal glucose tolerance at baseline[5]. Redefining threshold values of current diagnostic tools and incorporation of one-hour PG (1h-PG) levels may improve sensitivity of recognizing high-risk individuals earlier enough before advancement to permanent Dysglycemia.

Department of General Medicine, Government Medical College & Hospital, Chandigarh 160030
[1]MBBS, MD, Senior Resident and Corresponding Author
[2]MBBS, MD, Professor
[3]MBBS, MD, Resident

Received on : 02/07/2022
Accepted on : 20/07/2022

Currently, the utility of 1h-PG to predict overt Diabetes and related complications, including Nephropathy, Retinopathy, Neuropathy, Atherosclerosis, Fatty Liver and associated Mortality is underestimated while clinically evaluating metabolic Disease. This review may clarify the potential of 1h-PG in predicting Diabetes and subsequent complications and support its measurement in routine practice in an attempt to reduce the burden of Metabolic Dysglycemia.

Mechanism and Pathogenesis of Hyperglycemia related complications :

Long term exposure to unapparent chronic Hyperglycemia is now an identified marker for initiation of the pathogenesis of diabetic complications. Continuous glucose monitoring has shown that diabetic and pre-diabetic individuals have PG variability with one half of individuals having baseline hyperglycemic state[6]. We know that microvascular complications like retinopathy, nephropathy and neuropathy are majorly due to capillary endothelial dysfunction by chronic Hyperglycemia or glucose toxicity[7]. Hyperglycemia causes some major changes in a large vascular compartment that potentially promote accelerated Atherosclerosis, leading to macro-vascular complications. Sustained mild rise in glucose levels may also result in micro and macro-vascular complications. Presently, three crucial processes have arisen, that causes the majority of the patho-physiological alterations as detected in the vascular anatomy of diabetic individual : (1) Glycosylation of lipids and protein particles by non-enzymatic method, (2) Oxidative stress and (3) Activation of protein kinase C[8]. Oxidative stress occurs due to excess NADH and $FADH_2$ production by high glucose levels, leading to increased ATP/ADP ratio and mitochondrial dysfunction[9,10]. All these stress factors lead to end organ damage by direct or indirect mechanism.

Atherosclerosis and Endothelial Dysfunction :

The vital mechanism responsible for macro-vascular complications including Atherosclerosis in Hyperglycemia is the formation of advanced glycation end products by non-enzymatic interaction between glucose and lipoproteins or protein substances in arterial walls. Unusual activation of signalling cascades (such as protein kinase C), upgraded reactive oxygen species production and aberrant stimulation of hemodynamic regulation systems (such as the renin-angiotensin system) are another crucial mechanism[11-13]. Advanced glycation end products in non-haematopoietic cells have been linked with this complication[14]. Further, Flynn, *et al* demonstrated that Hyperglycemia is capable to start pathological alteration in bone marrow, leading to Myelopoiesis, monocytosis and accelerated plaque formation; even in the absence of overt diabetes or insulin resistance[15]. High glucose levels lead to activation of Intercellular Adhesion Molecule (ICAM)-1 and Vascular Cell Adhesion Molecule (VCAM)-1 due to hyperosmolar environment, which begin vascular endothelial dysfunctions[16]. Other than this, sub-clinical inflammatory process due to high PG also causes aberrant endothelial function[17]. All these mechanisms are associated with accelerated Atherosclerosis and microvascular complication, due to endothelial dysfunction.

Fatty Liver Disease :

Hyperglycemia leads to hepatic fat accumulation by various mechanisms and causes generation of fatty liver. Non-alcoholic Fatty Liver Disease (NAFLD) includes a bunch of liver disorders characterized by hepatic fat deposition (also called Steatosis) in the absence of insults like alcohol abuse and viral hepatitis, and is usually associated with a broad spectrum of the metabolic syndrome like impaired glucose tolerance or overt diabetes, visceral obesity, hypertension and dyslipidemia. Insulin resistance leads to free fatty acid release from adipose tissue, which leads to imbalance of lipid metabolism in the liver and hepatic mitochondrial dysfunction, causing hepatic inflammation and the development of fatty liver[18]. As Hyperglycemia is an indirect marker of insulin resistance, it is associated with fatty liver formation.

β-cell Dysfunction and Insulin Resistance :

Recently, Hyperglycemia is also associated with the development of insulin resistance. Hyperglycemia starts with β-cell dysfunction and this generates a pathological cycle, which leads to further β-cell abnormality and persistent raised PG levels. The mechanism for this β-cell dysfunction due to Hyperglycemia includes enhanced hexosamine flux, increased reactive Oxygen species, decreased Pdx-1 expression and increased pancreatic endoplasmic reticulum stress[19-22]. Impaired Pdx-1 activity leads to decreased insulin biosynthesis and increased β-cell apoptosis[23]. Even mild Hyperglycemia can promote β- cell dysfunction, due to changes in genetic structure and altered gene expression by glucose toxicity[24]. Madonna, *et al* have described that high glucose concentration and related hyperosmolar state can directly induce insulin resistance[25].

Importance of Unapparent Hyperglycemia :

American Diabetes Association sorted glucose intolerance on the ground of PG levels after a single 75-gm Oral Glucose Tolerance Test (OGTT). Pre-diabetes designated as fasting PG between: 100–125 mg/dl (Impaired Fasting Glucose) or impaired glucose tolerance with fasting PG levels <126 mg/dl but two-hour post load PG140–199 mg/dl and HbA1c between 5.7-6.4%[26]. It is superior to evaluate postprandial PG by 75gm OGTT than ordinary meal, because glucose rise after a meal is depending on the amount and type of the food which does not occur with OGTT. However, recent data has shown that even normal glucose tolerant individuals (individuals with normal two-hour post load plasma glucose) tend to have elevated cardio-vascular risk, as depicted by a worse plasma lipid levels, thickened intima-media, and hypertrophy of the left ventricular chamber[27]. Normal glucose tolerant individuals can have chronic Hyperglycemia, which can be missed by traditional tests like two-hour PG (2h-PG) level and HbA1c measurement. This continuous mild hyperglycemia is a prime precursor in the formation of biochemical and vascular abnormalities by inducing various functional, structural and metabolic derangements.

Hyperglycemia leads to a negative impact on β-cells of Pancreas, which is referred asglucotoxicity[28]. This deteriorates the secretory capability of β-cells[29,30]. Severe hyperglycemia affects β-cells more than milder Hyperglycemia[31]. In a study, subtle physiological Hyperglycemia led to deterioration in β-cell function and insulin resistance[32]. Another study showed that this insulin resistance due to chronic Hyperglycemia is largely irreversible[17]. Observations have also shown that insulin sensitivity in tissue was found to be 17% lower in individuals with upper levels of normal fasting PG range (90-97 mg/dl) compared with fasting PG <90 mg/dl[33]. Also, a progressive drop of initial first-phase insulin response can occur with fasting PG values between 90-97 mg/dl and further decline in late-phase insulin response at levels >108 mg/dl[34].

A study from Israel regarding glucose intolerance, Obesity and Hypertension with follow up for 24 years, demonstrated that individuals with a 1h-PG levels ≥155 mg/dl but with 2h-PG <140 mg/dl had significantly increased risk for both diabetes development and pre-diabetes conditions[35]. In the same study, 1h-PG levels >155 mg/dl was also established to anticipate mortality even when the 2h-PG was <140mg/dl. Myocardial damage and fatal ischemic heart disease and risk of microvascular complications like retinopathy were also considerably higher among individuals with elevated 1h-PG values.

A study by Succurro, *et al* found that one-hour post load PG levels >155mg/dl was an atherogenic condition and this cut off is useful in identifying high risk individuals[36]. Tanaka, *et al* using intimal medial thickness as a surrogate marker for Cardio-vascular disease demonstrated that deranged PG at one-hour was associated with increased intimal medial thickness more firmly than PG at two-hours, even in the absence of chronic Hyperglycemia[37]. These studies strongly represent the correlation of raising 1h-PG with cardiovascular complications.

Superiority of One-hour Post load Hyperglycemia:

Tabak, *et al* described a multilevel model theory related to an extended compensatory time interval prior to the clinical diagnosis of diabetes[38]. In this interval, insulin secretion in the body rises to compensate the ongoing development of resistance and this keeps PG values within normal range as a result of physiological adjustment. This leads to β-cell compensatory adaptation and later, generation of a brief unsteady time spell with a sharp rise of PG leading to overt diabetes. PG levels are within the normal physiological range for about 2-6 years during this period, before crossing the actual diagnostic cut-off for overt diabetes. Post load PG value, especially at one-hour may uncover the inconspicuous yet significant damage to β-cells in this time period.

Jagannathan, et al in their study, highlighted how HbA1c is an inferior marker, in terms of correlation with insulin sensitivity and β-cell function than single determinations of PG levels at one-hour[39]. The same study also explained that the 1h-PG value above 155 mg/dl had finer descriptive capability to point out high risk subjects, when compared with the present cut-off criteria for HbA1c. Also the Veterans study showed that the association of HbA1c with insulin sensitivity and β-cell dysfunction was a nonlinear association within the Mexican-American population[40]. This tells the ineffectiveness of HbA1c in the prediction of insulin sensitivity.

Similarly, studies have demonstrated that post prandial hyperglycemia is a causal factor in significant numbers of individuals with impaired glucose tolerance with normal levels of HbA1c, leading to increased cardiovascular morbidity[41,42]. It has been elucidated how subjects with an HbA1c level of 5.7-6.4% (pre-diabetic) and one-hour post load PG value above 155 mg/dl have a remarkably excess risk of hepatic steatosis when differentiated with subjects having pre-diabetic HbA1c levels, but one-hour post load PG value below 155 mg/dl[43]. This shows the inferiority of HbA1c

in terms of predicting fatty liver like complications. As HbA1c is an average of glucose values of the past 2-3 months, it cannot describe the daily post prandial rise or fluctuation in PG and this drawback can be abolished by using post load PG values.

Priya, *et al* found that both β-cell function and insulin sensitivity are altered among subjects with elevated 1h-PG values[44]. Sato, *et al* study suggested an abnormality in β-cell stimulus-secretion coupling process in the presence of an elevation of post challenge PG levels[45]. These studies promote the use of 1hPG for assessment of β-cell function. And it has been increasingly realized that, normal glucose tolerant individuals who have elevated 1h-PG >155 mg/dl, may have accelerated fatty liver disease development, subclinical inflammation and early atherosclerotic changes[36,46].

Yet another study has revealed that glycemic parameters measured by OGTT were more accurate in describing individuals with deranged β-cell function and described that the 1h-PG is better than HbA1c for this β-cell dysfunction[47]. The superiority of early Hyperglycemia identification is also proven by indirect evidence of complication reduction, after controlling hyperglycemia. Early diagnosis of dysglycemia or hyperglycemia can reduce relative risk of cardiovascular morbidity by 29% and all-cause mortality by 17% after 5 years[48]. Early detection of high-risk individuals is very crucial step to prevent the hyperglycemic injury and is imperative in younger individuals as they show a faster progression to diabetes than adults and have more life span[49]. Evaluating the young obese individuals with raised PG values at one-hour, may identify complications like Cardiomyopathy, neuropathy, nephropathy, atherosclerosis, and fatty liver at primordial stages. This strategy might prove crucial in maintaining and preserving β-cell function. Other than this, one-hour post load plasma glucose value measurement is easy and a feasible tool in developing countries and limited resource setting.

30-minute Post load Plasma Glucose : Another Emerging Marker :

Recently, Post load PG value at 30-minute has been evaluated to diagnose diabetes early and to assess its correlation with different end organ complications. A study on Japanese population showed that individuals with higher 30-minute post-load PG have increased risk of future diabetes development[50]. The study also described that the addition of 30-minute plasma value in standard OGTT can improve the future prediction. A study from India recently described the same finding and illustrated the predictive power of 30-minute PG value[51]. The study suggested that the 30-minute PG value of >188mg/dl was associated with future diabetes emergence, especially in obese population and with positive family history of diabetes. Further, one more analysis of Indian population including 753 participants illustrated the association of 30-minute post load PG and future diabetes development[52]. The study also observed that 30-minute PG value was an independent marker of future diabetes, superior to 2h-PG and HbA1c levels. These limited studies clearly indicate the importance of intermediate Hyperglycemia. However, more prospective studies and randomized trial are required for better insight regarding the use of 30-minute PG value and its incorporation in routine evaluation.

Conclusions

This review focuses on the correlation of after one-hour post load glycemic values with development future T2DM and its related various complications. Different observations have shown that one-hour Post-load Hyperglycemia is a better tool to distinguish the risk of diabetes development. This marker also carries the potential to identify high risk individuals earlier than other diagnostic markers like HbA1c and 2h-PG value. Deranged 1h-PG value reflects insulin resistance, an early step to abnormal fat metabolism and the formation of fatty liver. Studies have demonstrated that individuals with raised 1h-PG are pre-disposed to early Atherosclerosis development due to atherogenic lipid profile formation in the body and subsequent damage to the vessel wall. Individual with raised 1h-PG is also prone to the generation of reactive oxygen species and damage to the organs like liver, heart, kidney and retina. Currently, the 30-minute plasma glucose value is also emerging as a novel marker of future diabetes, but proper data is still less and require more extensive investigations. In this study, it is clear that one-hour post load Hyperglycemia is a strong marker in diagnosing diabetes and related complications and management of this parameter can independently prevent important organ damage.

References

1 Wild S, Roglic G, Green A, Sicree R, King H — Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27:** 1047-53.
2 Ebeling P, Koistinen HA, Koivisto VA — Insulin-independent glucose transport regulates insulin sensitivity. *FEBS Lett* 1998; **436:** 301-3.
3 Tuomilehto J — Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by charges in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344:** 1343-50.
4 Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler

PC — β-cell deficit and increased â-cell apoptosis in humans with type 2 diabetes. *Diabetes* 2003; **52:** 102-10.
5 Alberti KG, Zimmet PZ — Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15:** 539-53.
6 Hall H, Perelman D, Breschi A, Limcaoco P, Kellogg R, McLaughlin T, *et al* — Glucotypes reveal new patterns of glucose dysregulation. PLoS Biol. 2018;16:e2005143. https://doi.org/10.1371/journal.pbio.2005143
7 Brownlee M — The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005; **54:** 1615-25.
8 Nishikawa T, Edelstein D, Du XL, Yamagishi SI, Matsumura T, Kaneda Y, *et al*— Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 2000; **404:** 787-90.
9 Rains JL, Jain SK — Oxidative stress, insulin signaling, and diabetes. *Free Radic Biol Med* 2011; **50:** 567-75.
10 Tiwari BK, Pandey KB, Abidi AB, Rizvi SI — Markers of Oxidative Stress during Diabetes Mellitus. *J Biomark* 2013; **2013:** 378790.
11 Campos C — Chronic hyperglycemia and glucose toxicity: pathology and clinical sequelae. *Postgrad Med* 2012; **124:** 90-7.
12 Giacco F, Brownlee M — Oxidative stress and diabetic complications. *Circ Res* 2010; **107:** 1058-70.
13 Asmat U, Abad K, Ismail K — Diabetes mellitus and oxidative stress-A concise review. *Saudi Pharm J* 2016; **24:** 547-53.
14 Koulis C, Kanellakis P, Pickering RJ, Tsorotes D, Murphy AJ, Gray SP, *et al* — Role of bone-marrow- and non-bone-marrow-derived receptor for advanced glycation end-products (RAGE) in a mouse model of diabetes-associated atherosclerosis. *Clin Sci (Lond)* 2014; **127:** 485-97.
15 Flynn MC, Kraakman MJ, Tikellis C, Lee MKS, Hanssen NMJ, Kammoun HL, *et al* — Transient Intermittent Hyperglycemia Accelerates Atherosclerosis by Promoting Myelopoiesis. *Circ Res* 2020; **127:** 877-92.
16 Madonna R, Montebello E, Lazzerini G, Zurro M, De Caterina R — NA+/H+ exchanger 1- and aquaporin-1-dependent hyperosmolarity changes decrease nitric oxide production and induce VCAM-1 expression in endothelial cells exposed to high glucose. *Int J Immunopathol Pharmacol* 2010; **23:** 755-65.
17 Sun Q, Li J, Gao F — New insights into insulin: The anti-inflammatory effect and its clinical relevance. *World J Diabetes* 2014; **5:** 89-96.
18 Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H — Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. *World J Gastroenterol* 2009; **15:** 280-8.
19 Maedler K, Sergeev P, Ris F, Oberholzer J, Joller-Jemelka HI, Spinas GA, *et al* — Glucose-induced beta cell production of IL-1 beta contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* 2002; **110:** 851-60.
20 Marchetti P, Bugliani M, Lupi R, Marselli L, Masini M, Boggi U, *et al* — The endoplasmic reticulum in pancreatic beta cells of type 2 diabetes patients. *Diabetologia* 2007; **50:** 2486-94.
21 Maris M, Ferreira GB, D'Hertog W, Cnop M, Waelkens E, Overbergh L, *et al* — High glucose induces dysfunction in insulin secretory cells by different pathways: a proteomic approach. *J Proteome Res* 2010; **9:** 6274-87.
22 Tanaka Y, Gleason CE, Tran PO, Harmon JS, Robertson RP — Prevention of glucose toxicity in HIT-T15 cells and Zucker diabetic fatty rats by antioxidants. *Proc Natl Acad Sci USA* 1999; **96:** 10857-62.
23 Chen F, Sha M, Wang Y, Wu T, Shan W, Liu J, *et al* — Transcription factor Ets-1 links glucotoxicity to pancreatic beta cell dysfunction through inhibiting PDX-1 expression in rodent models. *Diabetologia* 2016; **59:** 316-24.
24 Ebrahimi AG, Hollister-Lock J, Sullivan BA, Tsuchida R, Bonner-Weir S, Weir GC — Beta cell identity changes with mild hyperglycemia: Implications for function, growth, and vulnerability. *Mol Metab* 2020; **35:** 100959.
25 Madonna R, Pieragostino D, Rossi C, Confalone P, Cicalini I, Minnucci I, *et al* — Simulated hyperglycemia impairs insulin signaling in endothelial cells through a hyperosmolar mechanism. *Vascul Pharmacol* 2020; **130:** 106678.
26 American diabetes association, Diagnosis and classiûcation of diabetes mellitus. *Diabetes Care* 2014; **37:** S81-S90.
27 Sciacqua A, Miceli S, Carullo G, Greco L, Succurro E, Arturi F, *et al* — One-hour postload plasma glucose levels and left ventricular mass in hypertensive patients. *Diabetes Care* 2011; **34:** 1406-11.
28 Rossetti L, Giaccari A, DeFronzo RA — Glucose toxicity. *Diabetes Care* 1990; **13:** 610-30.
29 Eizirik DL, Korbutt GS, Hellerström C — Prolonged exposure of human pancreatic islets to high glucose concentrations in vitro impairs the beta-cell function. *J Clin Invest* 1992; **90:** 1263-8.
30 D'Alessandris C, Andreozzi F, Federici M, Cardellini M, Brunetti A, Ranalli M, et al. Increased O-glycosylation of insulin signaling proteins results in their impaired activation and enhanced susceptibility to apoptosis in pancreatic beta-cells. *FASEB J* 2004; **18:** 959-61.
31 Boden G, Ruiz J, Kim CJ, Chen X — Effects of prolonged glucose infusion on insulin secretion, clearance, and action in normal subjects. *Am J Physiol* 1996; **270:** E251-8.
32 Merovci A, Tripathy D, Chen X, Valdez I, Abdul-Ghani M, Solis-Herrera C, *et al* — Effect of Mild Physiologic Hyperglycemia on Insulin Secretion, Insulin Clearance and Insulin Sensitivity in Healthy Glucose Tolerant Subjects. *Diabetes* 2021; **70:** 204-13.
33 Stancáková A, Javorský M, Kuulasmaa T, Haffner SM, Kuusisto J, Laakso M — Changes in insulin sensitivity and insulin release in relation to glycemia and glucose tolerance in 6,414 Finnish men. *Diabetes* 2009; **58:** 1212-21.
34 Godsland IF, Jeffs JAR, Johnston DG — Loss of beta cell function as fasting glucose increases in the non-diabetic range. *Diabetologia* 2004; **47:** 1157-66.
35 Bergman M, Chetrit A, Roth J, Jagannathan R, Sevick M, Dankner R — One-hour post-load plasma glucose level during the OGTT predicts dysglycemia: Observations from the 24 year follow-up of the Israel Study of Glucose Intolerance, Obesity and Hypertension. *Diabetes Res Clin Pract* 2016; **120:** 221-8.
36 Succurro E, Marini MA, Arturi F, Grembiale A, Lugarà M, Andreozzi F, *et al* — Elevated one-hour post-load plasma glucose levels identifies subjects with normal glucose tolerance but early carotid atherosclerosis. *Atherosclerosis* 2009; **207:** 245-9.
37 Tanaka K, Kanazawa I, Yamaguchi T, Sugimoto T. One-hour post-load hyperglycemia by 75g oral glucose tolerance test as a novel risk factor of atherosclerosis. *Endocr J* 2014; **61:** 329-34.
38 Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR — Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet* 2009; **373:** 2215-21.

39 Jagannathan R, Sevick MA, Fink D, Dankner R, Chetrit A, Roth J, *et al* — The 1-hour post-load glucose level is more effective than HbA1c for screening dysglycemia. *Acta Diabetol* 2016; **53:** 543-50.

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

41 Ning F, Zhang L, Dekker JM, Onat A, Stehouwer CD, Yudkin JS, *et al* — Development of coronary heart disease and ischemic stroke in relation to fasting and 2-hour plasma glucose levels in the normal range. *Cardiovasc Diabetol* 2012; **11:** 76.

42 DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001; **161:** 397-405.

43 Fiorentino TV, Andreozzi F, Mannino GC, Pedace E, Perticone M, Sciacqua A, *et al* — One-Hour Postload Hyperglycemia Confers Higher Risk of Hepatic Steatosis to HbA1c-Defined Prediabetic Subjects. *J Clin Endocrinol Metab* 2016; **101:** 4030-8.

44 Priya MM, Amutha A, Pramodkumar TA, Ranjani H, Jebarani S, Gokulakrishnan K, *et al* — β-Cell Function and Insulin Sensitivity in Normal Glucose-Tolerant Subjects Stratified by 1-Hour Plasma Glucose Values. *Diabetes Technol Ther* 2016; **18:** 29-33.

45 Sato Y, Oka R, Nakasone Y, Katakura M, Yamauchi K, Aizawa T— Impact of one-hour postchallenge glucose on the relationship between insulin sensitivity and secretion. *Endocr J* 2015; **62:** 573-83.

46 Sesti G, Hribal ML, Fiorentino TV, Sciacqua A, Perticone F — Elevated 1 h postload plasma glucose levels identify adults with normal glucose tolerance but increased risk of non-alcoholic fatty liver disease. *BMJ Open Diabetes Res Care* 2014; **2:** e000016.

47 Li C, Yang H, Tong G, Shen S, Feng W, Bi Y, *et al* — Correlations between A1c, fasting glucose, 2h postload glucose, and â-cell function in the Chinese population. *Acta Diabetol* 2014; **51:** 601-8.

48 Herman WH, Ye W, Griffin SJ, Simmons RK, Davies MJ, Khunti K, *et al* — Early Detection and Treatment of Type 2 Diabetes Reduce Cardiovascular Morbidity and Mortality: A Simulation of the Results of the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION-Europe). *Diabetes Care* 2015; **38:** 1449-55.

49 Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S — Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care* 2005; **28:** 902-9.

50 Hirakawa Y, Hata J, Yoshinari M, Higashioka M, Yoshida D, Shibata M, *et al* — 30-minute postload plasma glucose levels during an oral glucose tolerance test predict the risk of future type 2 diabetes: the Hisayama Study. *BMJ Open Diabetes Res Care* 2020; **8:** e001156.

51 Jagannathan R, Weber MB, Anjana RM, Ranjani H, Staimez LR, Ali MK, *et al* — Clinical utility of 30-min plasma glucose for prediction of type 2 diabetes among people with prediabetes: Ancillary analysis of the diabetes community lifestyle improvement program. *Diabetes Res Clin Pract* 2020; **161:** 108075.

52 Chamukuttan S, Ram J, Nanditha A, Shetty AS, Sevick MA, Bergman M, *et al* — Baseline level of 30-min plasma glucose is an independent predictor of incident diabetes among Asian Indians: analysis of two diabetes prevention programmes. *Diabetes Metab Res Rev* 2016; **32:** 762-7.