The shape of the glucose response curve during an OGTT heralds β−cell function in a large Chinese population

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Abstract

Background The shape of the glucose response during an oral glucose tolerance test can detect β-cell function and insulin resistance. But there were few studies in Chinese, so we aimed to verify the utility of these connections in a large Chinese population. Methods A total of 11,866 times of 3-h OGTT were categorized to either a monophasic or a multiphasic group based on the shape of the glucose response. Homeostasis model assessments of fasting insulin resistance, Matsuda index, insulinogenic index and the disposition index were assessed by plasma glucose and serum insulin concentration obtained at fasting or during an OGTT. Results Individuals with a monophasic shape had significantly higher glucose, insulin, and had significantly lower insulin sensitivity and impaired β-cell function than multiphasic group. In addition, Individuals were younger with a multiphasic shape compared to those with a monophasic shape. Conclusion The monophasic OGTT glucose response curve could reflect impaired β-cell function in a large Chinese population.

Background

The cause of diabetes mellitus can be summarized as defecting in β-cell function and insulin action (i.e. hepatic and/or peripheral insulin sensitivity) or both. It is widely accepted that the gold standard method for evaluating insulin action is Hyperinsulinemic-euglycemic-clamp[1]. Because this kind of method is invasive, complicated and expensive, its application in the clinical practice is limited. The oral glucose tolerance test (OGTT) had been used to diagnose type 2 diabetes (T2D) or to capture the impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) based on the fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG)[2]. Although β-cell function and insulin action can be obtained through calculating a series of formula, such as insulinogenic index or Matsuda Index during the OGTT, it is not intuitive. The OGTT glucose response curve can be a novel and intuitive biomarker to identify early metabolic risk[3]. Recent cross-sectional studies[3-10] showed that OGTT response curves, either monophasic or biphasic, can not only detect β-cell function and insulin resistance, but also differentiate diabetes risk. Those studies revealed that individuals with a monophasic curve tended to have worse insulin sensitivity and β-cell function. A recent prospective study demonstrated that individuals with a biphasic curve developed T2D at a lower rate than those with a monophasic curve independently of FPG and/or 2hPG[11].

However, the scale of these studies was generally small with maximum hundreds of subjects included and only one study was conducted in Asian populations[8]. These studies mainly focused on people without diabetes. No studies showed a relationship between age and the shape of glucose response curve. In addition, few studies reported the dynamic change of glucose response curves and its relationship with the baseline β-cell function and insulin sensitivity.

Therefore, the purposes of this study were as follows: 1) to verify the utility of the OGTT glucose response curve on predicting β-cell function and insulin sensitivity in a large Chinese population with different status of glucose tolerance; 2) to exam the relationship between age and the shape of glucose response curves ; 3) to assess if the shape of glucose response curves change dynamically over time and whether the change was related with the baseline β-cell function and insulin sensitivity.

Materials And Methods

Subjects

We retrospectively analyzed data of individuals who were tested with a 3-h OGTT and with complete data of glucose and insulin in Peking Union Medical College Hospital from August 2011 to January 2018. Participants were excluded from the study if any of the following criteria were met: a) missing demographic information (age or sex); b) fasting plasma glucose<3.9mmol/L; c) use of insulin at the time of OGTT; d) fasting serum insulin >60uIU/ml or serum insulin level greater than 300uIU/ml at any point of OGTT because the test upper limit was 300uIU/ml; e) 30 minute plasma glucose was less of equal to 0 minute plasma glucose or 30 minute serum insulin was less of equal to 0 minute serum insulin to insure insulinogenic index could be calculated; f) Shapes which could not be classified.

Blood sampling and OGTT

After an overnight fast, participants underwent a 3-h OGTT (1.75 g/kg, maximum 75 g). Venous blood samples were obtained at 0, 30, 60, 120, and 180min. Plasma glucose was measured by the hexokinase method using a Beckman AU2700 analyzer (Beckman Coulter, Brea, CA, USA). Serum insulin was assessed by chemiluminescence immunoassay using a Siemens ADIVA Centaur XP analyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). The glucose and insulin assays were standardized to NIST SRM 965 and WHO 1st IRP 66/304, respectively. The repeatability and within laboratory coefficient variations (CV) were less than 5%.

Classification of glucose tolerance status

According to the World Health Organization definition, normal glucose tolerance (NGT) was defined as fasting plasma glucose< 6.1mmol/L and 2-h plasma glucose<7.8mmol/L. Prediabetes was defined as having IFG (fasting plasma glucose: 6.1–6.9mmol/L) and/or IGT (2-h plasma glucose: 7.8-11.0mmol/L). Diabetes was defined as having either FPG ≥7.0mmol/l and/or 2-h plasma glucose ≥11.1mmol/l.

Classification of glucose curve shapes

The shapes were classified in line with previous studies[12]. This was done with a plasma glucose threshold of 0.25mmol/L to minimize fluctuations in glucose concentrations, which may be caused by the method of glucose analysis rather than physiological reasons. A monophasic response curve was determined by a gradual increase in glucose concentrations until a peak was reached followed by a subsequent decrease. A biphasic response curve was defined by a second rise in glucose concentrations. A triphasic response curve was defined by 2 complete peaks of the plasma glucose curve. The latter two were collectively called multiphasic response curve.

Calculation of variables

Areas under the glucose and insulin curves were calculated with the trapezoidal rule[7]. Insulin action was estimated by the homeostasis model assessment for insulin resistance(HOMA-IR) and the whole-body insulin sensitivity index of Matsuda. HOMA-IR=(I_0-G_0)/22.5, with glucose and insulin expressed as mmol/l and mUI/ml respectively[13]. The Matsuda index = 10000/√[(fasting glucose (mg/dl) × fasting insulin (μU/ml)) ×(mean glucose (mg/dl) × mean insulin (μU/ml)][14]. Insulin secretion was estimated by the insulinogenic index. The

insulinogenic index was calculated using fasting and 30-min insulin and glucose concentrations[15]. β-cell function was estimated by the disposition index as the product of insulinogenic index and HOMA-IR[16].

Statistical Analysis

Summary statistics were calculated using frequencies and proportions for categorical data and means (SDs) for continuous variables. Unpaired Student's t, Pearson χ^2 and Kruskal-Wallis tests were used for comparisons. ANCOVA was used to compare two glucose response curve groups (monophasic vs. multiphasic) after adjusting for the potential confounding effects (age, sex, glycemic status). A two sided p value < 0.05 was used for statistical significance.

All data was analyzed using IBM SPSS Statistics, version 25. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline characteristics according to glucose curve shapes

11,866 times of OGTT among 11,036 study individuals were included in the final analysis (Figure 1). The baseline age was 38.7±14.5 years and 70.7% were female. In terms of the shape of OGTT glucose response curve, 88.3% were monophasic, 5.7% were biphasic and 6.0% were triphasic. Although the individuals with triphasic curve had better insulin sensitivity and ββ-cell function than the biphasic curve (Table1), in view of the limited cases, the triphasic group and the biphasic group were collectively referred to as multiphasic group. Physical and glucose metabolic characteristics of participants with monophasic and multiphasic curves were presented in Table 2. There was no difference in age between the two groups. The monophasic group exhibited significantly higher FPG, 2hPG, fasting serum insulin (FINS), 2h serum insulin (2h INS) compared with the multiphasic group. The monophasic group had significantly higher HOMA-IR and lower Matsuda index and insulinogenic index. As the indicator of the β-cell function, the disposition index was nearly 42% lower in the monophasic group (Table 2). These differences remained significant after adjusting for sex and age.

Comparison of the glucose curve shapes among different age group

To explore the relationship between age and the shape of OGTT curve, we divided age into 6 categories (Figure 2). We found that higher proportion of younger people belonged to multiphasic group, i.e. significantly higher proportion of participants with age less than 20 or 20 to 30 years were in multiphasic group compared with all the other older groups (P<0.001). Furthermore, we divided each age group into three glycemic stage (NGT, prediabetes, DM) to adjust the effect of age on glycemic status (Figure 3). When participants were in NGT or prediabetes, younger individuals had higher proportion of multiphasic curves. But when the glycemic status progressed to diabetes, quite low percentage of individuals were with multiphasic curves in all age groups.

Types of glucose curve shape as the indicator for insulin resistance and βcell function

Surrogate markers of insulin sensitivity and ββ-cell function including HOMA-IR, Matsuda Index, insulinogenic index and disposition index were significantly different between the monophasic and multiphasic groups (Table

2). After stratification in the glycemic status, the difference in insulinogenic index remained significantly in every status of the glycemic metabolism. However, the other three indexes had no longer significant difference in individuals who had DM. In addition, no significant differences were noted for HOMA-IR in participants who were in prediabetes between the two groups (Table 3).

OGTT glucose nadir time in relation to insulin resistant and βcell function

The multiphasic group can be further divided into two categories by the time when glucose is lowest. The triphasic curve all reached the nadir at 1 hour, the biphasic curve's nadir time can be 1 hour or 2 hours. As for β-cell function, the curve whose nadir time is 2h had significantly lower insulinogenic index and disposition index (Table 4). But there is no marked difference between the two groups for the HOMA-IR and Matsuda Index.

Change of the OGTT glucose curve shape and risk of impaired glucose metabolism

There were 635 people undergoing twice OGTT. Table 5 shows baseline physical and metabolic characteristics of all the participants with stable shape respect with those with unstable shape. 80.3% of the participants own unchanged OGTT glucose response curve shape at baseline and the second time (Table 5). Individuals who maintained a monophasic response glucose curve had a lowest rate of NGT and those who maintained a multiphasic response glucose curve had a highest rate of NGT at baseline. Individuals with a stable monophasic glucose response shape had significantly highest fasting and 2h plasma glucose. Persistence of the monophasic shape was in general associated with worst insulin sensitivity and reduced ββ-cell function. Individuals whose response glucose curve changed from multiphasic to monophasic tended to have a higher rate of deterioration in glucose metabolism (Table 6).

Discussion

The present investigation revealed the following findings for the shape of OGTT curve in a large Chinese population: 1) multiphasic OGTT response curves were not rare in Chinese people which accounted for more than 10% of the population; 2) monophasic curves were more common in older people and in worse glycemic status; 3) individuals with monophasic curves had poorer β-cell function than individuals with multiphasic curves, despite having similar glycemic status; 4) individuals who were in NGT with a monophasic shape showed significantly worse insulin sensitivity, as reflected by the HOMA-IR and Matsuda index, compared to patients with a multiphasic curve；5) β-cell function was better in patients whose glucose concentration started to decrease at 60min than later among the multiphasic curve group; 6) number of phases of the same subject could change at different times, and the number of phases increased with the improvement of glucose status.

In the studies of non-diabetic individuals, morphology of the monophasic response glucose curve is the dominant phenotype, up to 57-84% in adults[9, 10, 12, 17, 18] and 35-69% in obese youth at high risk for T2D[3, 4, 6, 7, 19]. Our study showed that about 88.3% individuals were with monophasic response curves and 11.7% individuals were with multiphasic response curves. Combining our present research with previous studies in youth[3, 7] and adults[9], the multiphasic group tend to be associated with younger age compared with the monophasic group. Our study further found that there was little difference between the two glucose curve shape groups when the

glycemic status reached diabetes, and both youth and adults had extremely low proportion of multiphasic OGTT response curve.

Cross-sectional studies in youth[3-10] and adults[8-10, 18] showed that the shape of the OGTT glucose response curve could indicate insulin sensitivity and β-cell function, as well as differentiate type 2 diabetes risk. Obese youths with monophasic glucose response curves were worse in both hepatic and peripheral insulin sensitivity measured by the clamp method compared with the biphasic group, as well as β-cell function which was presented as impaired disposition index as a result of lacking in compensatory increase in first and second-phase insulin secretion[3]. Evidence from patients with suspected gestational diabetes who underwent 3h OGTT showed that a greater number of phases in the OGTT glucose response curve was associated with a healthier metabolic state, which suggested that a biphasic response curve may associated with a lower incidence of prediabetes and T2D[10]. β-cell function was better in individuals with multiphasic glucose response curve in our study. As for the insulin sensitivity, the difference was still significant in NGT group, but the difference did not remain significant in diabetes group. The most likely reason is the defects in ββ-cell function are more severe in Chinese patients with diabetes than Europe or USA, resulting in more serious deficiencies in insulin secretion[20].

A United States study which conducted in adult patients showed that the baseline and the subsequent glucose concentrations in the OGTT could stratify the risk for progression to T2D, expressed as a faster return to the FPG concentration may suggested a lower risk of T2D[17]. Our study further found individuals with multiphasic curves whose plasma glucose concentration reached the lowest point at 60 min had better β-cell function than those with a nadir at 120 min.

Our data showed that Individuals whose response glucose curve changed from multiphasic to monophasic during follow-up were more prone to deteriorate in glycemic status than whose glucose response curves were changed from monophasic curves to multiphasic curves, which were supported by several longitude studies. A 7-8 year longitude study demonstrated that, individuals with monophasic curves had twice the incidence of diabetes than individuals with biphasic curves in pre-diabetic patients despite similar fasting and 2-h plasma glucose concentrations[17]. Individuals with a monophasic curve at baseline, and in those whose patterns change from biphasic to monophasic had an increased risk for impaired glucose metabolism[11]. We also found individuals persistent with monophasic curve had worst insulin sensitivity and β-cell function than other forms at baseline.

The strengths of the present investigation include the following: 1) a first-time large-scale up to ten thousand in investigating the relationship between OGTT glucose response curve and insulin resistance/β-cell function in Chinese; 2) the study included people with different glucose metabolic states and across different age groups. Potential perceived limitations would be that we have no data on anthropometry data, such as BMI, waist circumference, which could have influence on glycemic status. But previous research showed that the OGTT response curve shape remained a stronger association with insulin sensitivity and β-cell function after adjusting for BMI, BP and waist circumference[3, 5]. In addition, the OGTT-glucose response curve shape was determined by 0min, 30min, 60min, 120min, 180min and lack of 90min glucose data, which may underestimate the phase of the curve. Investigations on the change of patterns or shapes of the OGTT-glucose response curves did not have a regular follow-up.

CONCLUSIONS

In summary, the current study is the first to demonstrate that in a large Chinese population, the monophasic OGTT glucose response curve was associated with reduced β-cell function. However, prospective longitudinal studies are needed to verify the value of the OGTT-glucose response curve in predicting progression to prediabetes or type 2 diabetes in Chinese. Further, it remains essential to examine whether any factors could shift the OGTT-glucose response curve from monophasic to multiphasic.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the ethical rules of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Peking Union Medical College Hospital.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Cheng, Zhang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cheng, Yang Zhang, and Yuxiu Li. Acquisition of data: Cheng and Qiu. Analysis and interpretation of data: Cheng, Yang, Zhang. Drafting of the manuscript: Yang,

Cheng and Zhang. Critical revision of the manuscript for important intellectual content: Cheng, Na Yang, Qiu, Xu, Ping, Wei Li, Sun, Zhang, Yuxiu Li. Statistical analysis: Cheng, Yang and Zhang. Obtained funding: Zhang. Administrative, technical, and material support: Cheng, Yang and Zhang. Study supervision: Cheng, Zhang and Yuxiu Li. All authors have approved the final article.

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References

1. Heise, T., et al., *Euglycaemic glucose clamp: what it can and cannot do, and how to do it.* Diabetes Obes Metab, 2016. 18(10): p. 962-72.

2. Jia, W., et al., *Standards of medical care for type 2 diabetes in China-0027.* Diabetes Metab Res Rev, 2019: p. e3158.

3. Kim, J.Y., et al., *The Shape of the Glucose Response Curve During an Oral Glucose Tolerance Test Heralds Biomarkers of Type 2 Diabetes Risk in Obese Youth.* Diabetes Care, 2016. 39(8): p. 1431-9.

4. Bervoets, L., A. Mewis, and G. Massa, *The shape of the plasma glucose curve during an oral glucose tolerance test as an indicator of Beta cell function and insulin sensitivity in end-pubertal obese girls.* Horm Metab Res, 2015. 47(6): p. 445-51.

5. Herrera-Martinez, A.D., et al., *[The monophasic pattern in oral glucose tolerance test as a predictive risk factor of type 2 diabetes in obese paediatric patients].* An Pediatr (Barc), 2017. 87(4): p. 211-217.

6. Kim, J.Y., et al., *Glucose response curve and type 2 diabetes risk in Latino adolescents.* Diabetes Care, 2012. 35(9): p. 1925-30.

7. Nolfe, G., et al., *Beyond the morphology of the glucose curve following an oral glucose tolerance test in obese youth.* Eur J Endocrinol, 2012. 166(1): p. 107-14.

8. Kanauchi, M., et al., *Betaβ-cell function and insulin sensitivity contribute to the shape of plasma glucose curve during an oral glucose tolerance test in non-diabetic individuals.* Int J Clin Pract, 2005. 59(4): p. 427-32.

9. Tschritter, O., et al., *Assessing the shape of the glucose curve during an oral glucose tolerance test.* Diabetes Care, 2003. 26(4): p. 1026-33.

10. Tura, A., et al., *Shape of glucose, insulin, C-peptide curves during a 3-h oral glucose tolerance test: any relationship with the degree of glucose tolerance?* Am J Physiol Regul Integr Comp Physiol, 2011. 300(4): p. R941-8.

11. Manco, M., et al., *Shape of the OGTT glucose curve and risk of impaired glucose metabolism in the EGIR-RISC cohort.* Metabolism, 2017. 70: p. 42-50.

12. Ismail, H.M., et al., *The shape of the glucose concentration curve during an oral glucose tolerance test predicts risk for type 1 diabetes.* Diabetologia, 2018. 61(1): p. 84-92.

13. Matthews, D.R., et al., *Homeostasis model assessment: insulin resistance and betaβ-cell function from fasting plasma glucose and insulin concentrations in man.* Diabetologia, 1985. 28(7): p. 412-9.

14. Matsuda, M. and R.A. DeFronzo, *Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp.* Diabetes Care, 1999. 22(9): p. 1462-70.

15. Kosaka, K., et al., *Insulin secretory response of diabetics during the period of improvement of glucose tolerance to normal range.* Diabetologia, 1974. 10(6): p. 775-82.

16. Retnakaran, R., et al., *Evaluation of proposed oral disposition index measures in relation to the actual disposition index.* Diabet Med, 2009. 26(12): p. 1198-203.

17. Abdul-Ghani, M.A., et al., *The shape of plasma glucose concentration curve during OGTT predicts future risk of type 2 diabetes.* Diabetes Metab Res Rev, 2010. 26(4): p. 280-6.

18. Trujillo-Arriaga, H.M. and R. Roman-Ramos, *Fitting and evaluating the glucose curve during a quasi continuous sampled oral glucose tolerance test.* Comput Biol Med, 2008. 38(2): p. 185-95.

19. Arslanian, S., et al., *The Shape of the Glucose Response Curve During an Oral Glucose Tolerance Test: Forerunner of Heightened Glycemic Failure Rates and Accelerated Decline in betaβ-cell Function in TODAY.* Diabetes Care, 2019. 42(1): p. 164-172.

20. Jia, W., *Diabetes research in China: making progress.* Lancet Diabetes Endocrinol, 2017. 5(1): p. 9-10.

Tables

Table 1 Demographic and metabolic characteristics of 1387 participants with biphasic versus triphasic

Variables	Biphasic group (n = 675)	Triphasic group (n=712)	P value
Age（years）	34.1±14.9	35.0±14.4	0.227
Sex（male/female）（n%）	147（21.8）/528（78.2）	152（21.3）/560（78.7）	0.846
FBG（mmol/L）	5.3±0.6	5.2±1.9	0.137
2h GLU（mmol/L）	5.5±1.9	7.3±2.1	<0.001
FINS	13.5±8.7	14.0±7.7	0.263
2h INS	55.3±44.2	98.2±62.8	<0.001
Glycemic status(%)			
NGT	86.5	67.7	
IFG/IGT/IFG+IGT	10.1	27.1	<0.001
DM	3.4	5.2	
Glucose AUC ($mg \cdot dL^{-1} \cdot h^{-1}$)	1199.4±277.0	1197.1±287.0	0.881
Insulin AUC($mg \cdot dL^{-1} \cdot h^{-1}$)	13095.8±7437.8	14827.6±7713.3	<0.001
HOMA-IR	3.2±2.2	3.3±1.9	0.516
Matsuda Index	4.0±3.3	3.5±2.2	0.002
Insulinogenic index	14.0±16.4	19.8±20.7	<0.001
Disposition index	15.0±29.3	19.1±21.5	0.002

OGTT-glucose response curve

Values are reported as the mean±SD or n (%).

Table2 Demographic and metabolic characteristics of 11,866 participants with monophasic versus multiphasic OGTT glucose response curve

Variables	Monophasic group (n = 10479)	Multiphasic group (n=1387)	P value	Adjusted P value*
Age（years）	39.3±14.4	34.6±14.7	0.122	
Sex（male/female）（n%）	3176(30.3)/7303(69.7)	299(21.6)/1088(78.4)	<0.001	
FBG（mmol/L）	5.8±1.4	5.2±1.7	<0.001	
2h GLU（mmol/L）	8.8±3.9	6.5±2.2	<0.001	
FINS	14.5±8.7	13.8±8.2	0.002	
2h INS	102.7±66.8	77.3±58.6	<0.001	
Glycemic status(%)				
NGT(%)	47.7	76.9		
IFG/IGT/IFG+IGT(%)	29.5	18.8	<0.001	
DM(%)	22.8	4.3		
Glucose AUC ($mg \cdot dL^{-1} \cdot h^{-1}$)	1567.2±533.4	1198.2±282.1	<0.001	
Insulin AUC($mg \cdot dL^{-1} \cdot h^{-1}$)	15494.4±8421.1	13984.8±7627.0	<0.001	
HOMA-IR	3.8±2.7	3.2±2.0	<0.001	<0.001
Matsuda Index	3.0±1.9	3.8±2.8	<0.001	<0.001
Insulinogenic index	11.6±14.1	17.0±18.9	<0.001	<0.001
Disposition index	8.0±11.8	17.1±25.6	<0.001	<0.001

Values are reported as the mean±SD or n (%). *P value after adjusted for age and sex.

Table 3 Demographic and metabolic characteristics of 11,866 participants with monophasic versus multiphasic OGTT-glucose response curve in different glycemic status

NGT（n=6063）			Prediabetes（n=3348）			DM（n=2454）		
Monophasic(n=4997)	Multiphasic(n=1066)	P	Monophasic (n=3087)	Multiphasic (n=261)	P	Monophasic (n=2394)	Multiphasic (n=60)	P
34.5±13.1	32.4±13.5	<0.001	41.8±14.1	40.3±16.4	0.113	45.8±14.1	47.0±14.9	0.535
1196(23.9)/3801(76.1)	206(19.3)/860(80.7)	0.001	954(30.9)/2133(69.1)	76(29.1)/185(70.9)	0.577	1026(42.9)/1368(57.1)	17(28.3)/43(71.7)	0.025
5.1±0.5	5.1±0.4	<0.001	5.7±0.7	5.6±0.6	0.001	7.4±2.1	6.8±1.5	0.016
6.1±0.9	5.7±1.2	<0.001	8.7±1.2	8.3±1.4	<0.001	14.5±3.9	12.7±3.4	0.001
13.8±8.2	13.4±8.0	0.139	15.0±8.5	15.2±8.8	0.609	15.5±9.8	14.5±7.8	0.443
87.6±57.6	67.9±51.4	<0.001	127.8±69.6	112.3±69.7	0.001	102.2±71.4	92.4±64.7	0.295
1200.8±158.1	1099.4±153.7	<0.001	1572.1±166.0	1403.2±168.3	<0.001	2326.5±547.5	2061.9±444.3	<0.001
15303.1±7845.3	13354.1±7200.9	<0.001	17498.1±8698.0	16665.3±8684.1	0.237	13316.3±8622.4	13529.8±7683.7	0.849
3.2±1.9	3.0±1.9	0.038	3.8±2.2	3.8±2.3	0.834	5.1±3.8	4.4±2.6	0.117
3.3±2.0	4.0±3.0	<0.001	2.6±1.7	2.9±1.5	0.030	2.6±1.9	2.9±2.3	0.170
32.9±26.7	47.4±43.3	<0.001	17.9±13.4	31.3±25.2	<0.001	7.8±7.1	12.7±10.5	<0.001
12.5±15.3	19.6±28.5	<0.001	5.5±4.4	10.0±8.2	<0.001	2.0±2.1	3.7±3.4	0.535

Values are reported as the mean±SD or n (%).

Table4 Demographic and metabolic characteristics of 1387 participants with OGTT glucose nadir at 60min versus at 120min

	OGTT glucose nadir at 60min (n=823)	OGTT glucose nadir at 120min (n=564)	P
Age（years）	34.4±14.5	34.8±15.0	0.680
Sex（male/female），n%	168(20.4)/655(79.6)	131(23.2)/433(76.8)	0.232
FBG（mmol/L）	5.2±0.7	5.3±0.7	0.063
2h GLU（mmol/L）	7.2±2.2	5.4±1.7	<0.001
FINS	14.0±7.9	13.4±8.5	0.145
2h INS	94.0±62.5	53.0±41.7	<0.001
Glycemic status(%)			
NGT(%)	69.6	87.4	
IFG/IGT/IFG+IGT(%)	25.2	9.6	<0.001
DM(%)	5.2	3.0	
Glucose AUC (mg·dL^{-1}·h^{-1})	1191.0±298.5	1208.7±256.2	0.249
Insulin AUC(mg·dL^{-1}·h^{-1})	14526.7±7747.6	13193.9±7383.2	0.001
HOMAIR	3.3±1.9	3.2±2.1	0.324
Matsuda Index	3.7±3.0	3.8±2.4	0.532
Insulinogenic index	50.5±45.1	31.7±29.5	<0.001
Disposition index	19.7±22.1	13.3±29.7	<0.001

Values are reported as the mean±SD or n (%).

Table 5 Demographic and metabolic characteristics of 635 participants with stable versus unstable OGTT-glucose response curve

	Stable		Unstable		P value
	Monophasic	Multiphasic	Monophasic to Multiphasic	Multiphasic to Monophasic	
N	498	12	58	67	
Age（years）	36.7±13.0	37.3±12.6	34.6±14.0	33.9±14.3	0.817
Sex（male/female）%）	97（19.5）/401（80.5）	3（25.0）/9（75.0）	10（17.2）/48（82.8）	9（13.4）/58（86.8）	0.612
FBG（mmol/L）	5.6±1.0	5.3±0.6	5.2±0.6	5.2±0.5	0.001
2h GLU（mmol/L）	8.4±2.9	5.7±1.5	6.6±1.7	6.4±1.7	<0.001
FINS	16.3±9.1	11.9±6.0	15.1±9.8	16.8±9.6	0.327
2h INS	121.0±71.0	84.6±72.9	101.6±67.3	92.0±64.5	0.205
Glycemic status(n,%)					
NGT	225（45.2）	10（83.3）	44（75.9）	50（74.6）	
IFG/IGT/IFG+IGT	195（39.2）	2（16.7）	13（22.4）	17（25.4）	<0.001
DM	78（15.7）	0（0）	1（1.7）	0（0）	
Glucose AUC (mg·dL^{-1}·h^{-1})	1499.6±396.8	1122.0±138.7	1246.4±253.5	1186.7±208.1	<0.001
Insulin AUC(mg·dL^{-1}·h^{-1})	17801.9±8795.1	15526.4±8408.6	17491.7±8900.3	16747.8±8470.6	0.404
HOMA-IR	4.1±2.5	2.8±1.5	3.6±2.4	3.9±2.3	0.413
Matsuda Index	2.7±1.7	3.6±2.2	3.1±1.9	3.1±1.9	0.196
Insulinogenic index	26.6±26.9	48.6±32.0	36.4±24.0	54.2±57.3	0.001
Disposition index	8.0±8.9	25.2±33.4	13.8±12.2	18.1±23.0	<0.001

Values are reported as the mean±SD or n (%).

Table 6 The relationship between the change of the phase number and the change of the glycemic status

Glycemic status		Improve	Unchanging	Aggravation	Total
Change of the phase-number	Decrease	9（13.4%）	47（70.1%）	11（16.4%）	67
	Unchanging	98（19.2%）	316（62.0%）	96（18.8%）	510
	Increase	12（20.7%）	38（65.5%）	8（13.8%）	58
Total		119	401	115	635

Values are reported as N (n%).

Figures

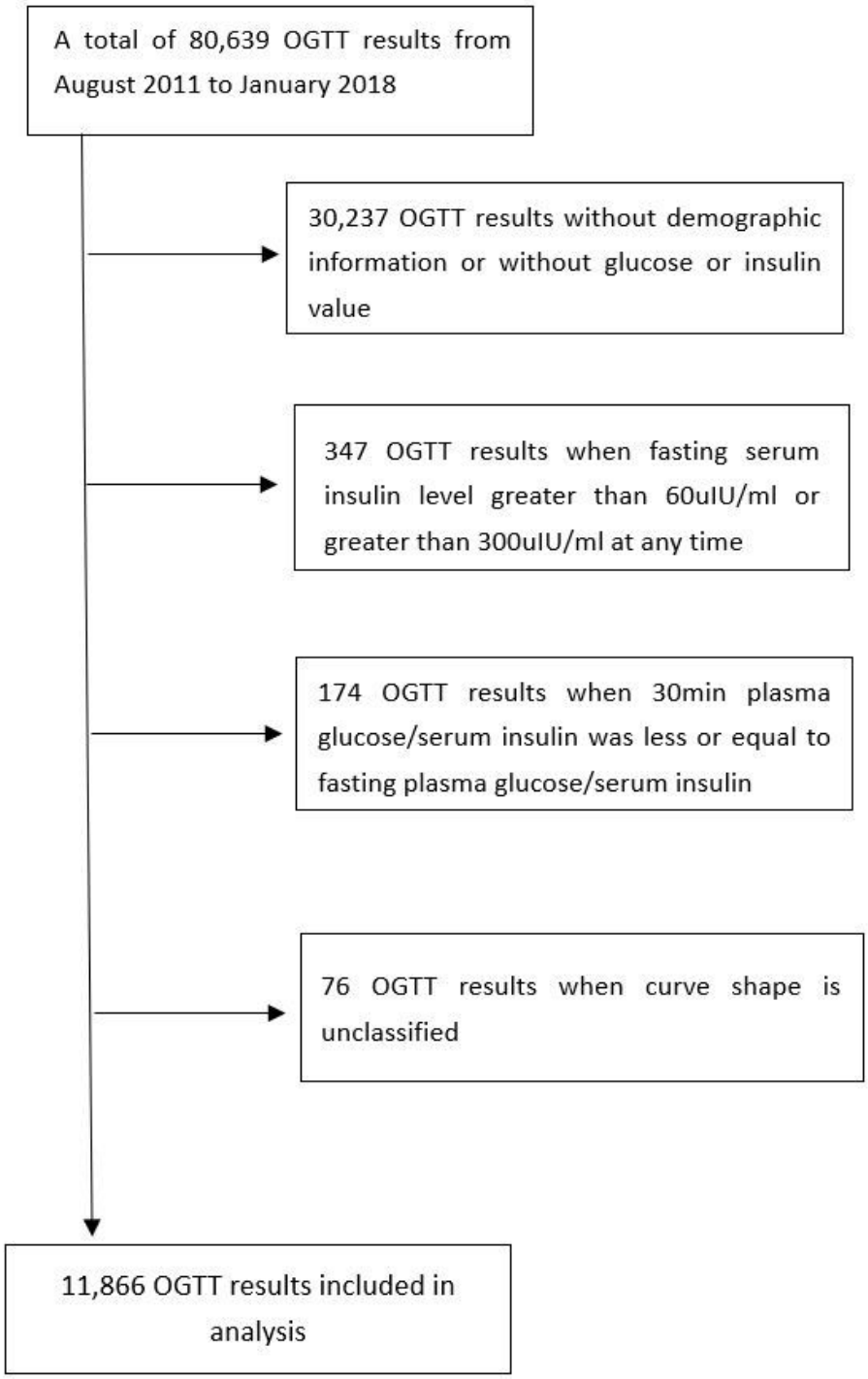

Figure 1

Study Flow Diagram OGTT: oral glucose tolerance test

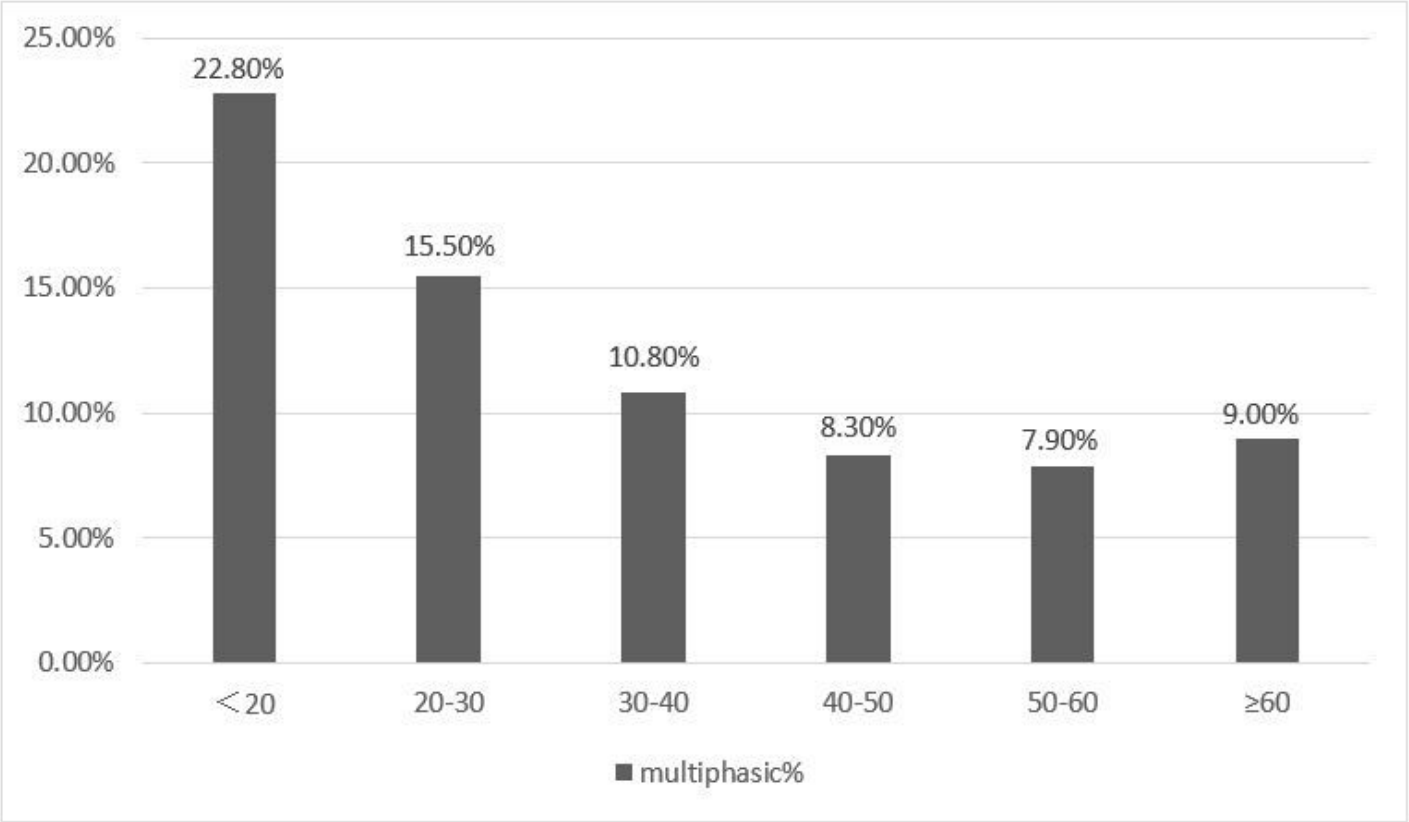

Figure 2

Proportion of multiphasic curves at different age group

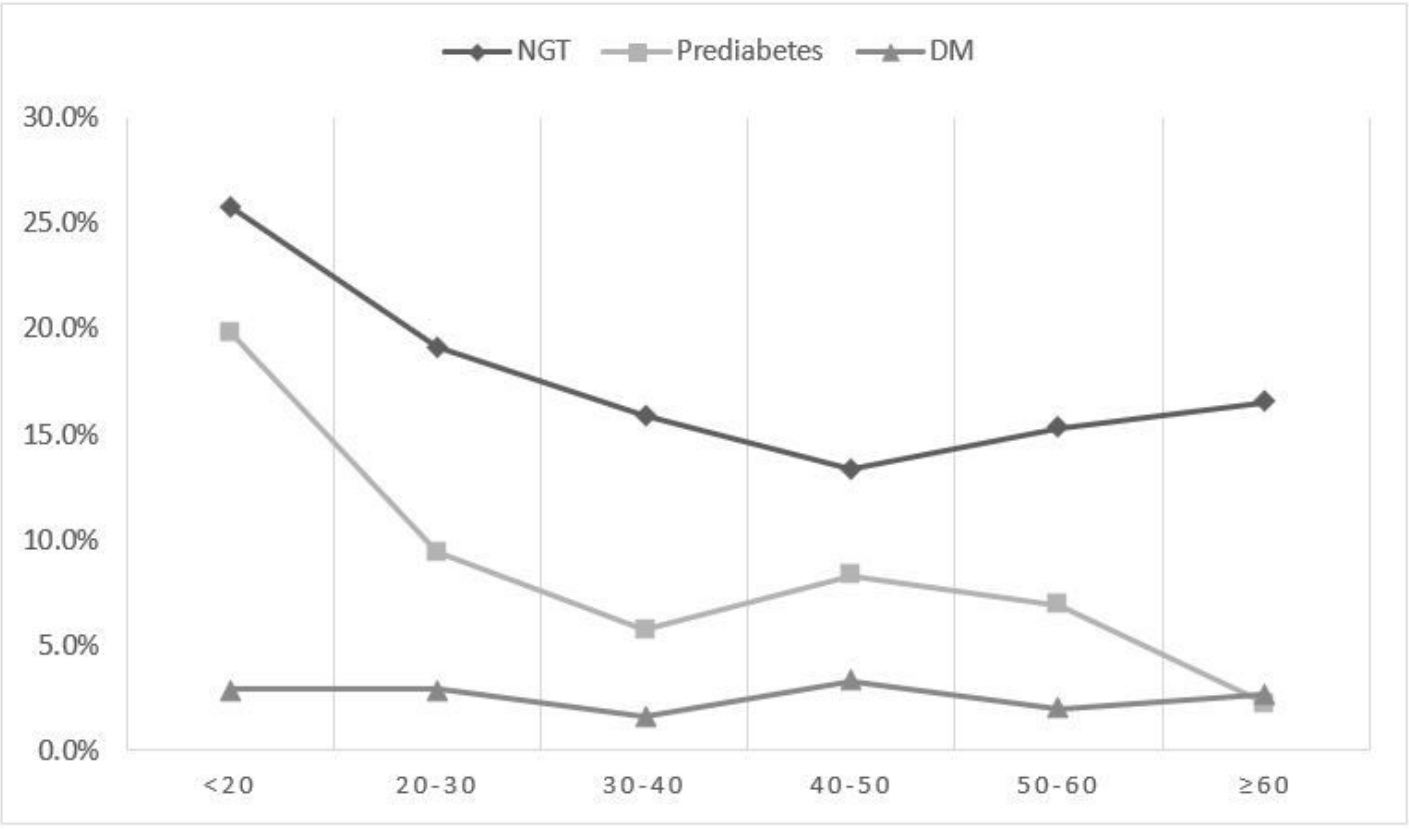

Figure 3

Proportion of multiphasic curves at different age group and glycemic status