Targeted metabolomic analysis reveals the association between the postprandial change in palmitic acid, branched-chain amino acids and insulin resistance in young obese subjects

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ABSTRACT

Obesity is the result of a positive energy balance and often leads to difficulties in maintaining normal postprandial metabolism. The changes in postprandial metabolites after an oral glucose tolerance test (OGTT) in young obese Chinese men are unclear. In this work, the aim is to investigate the complex metabolic alterations in obesity provoked by an OGTT using targeted metabolomics. We used gas chromatography–mass spectrometry and ultra high performance liquid chromatography–triple quadrupole mass spectrometry to analyze serum fatty acids, amino acids and biogenic amines profiles from 15 control and 15 obese subjects at 0, 30, 60, 90 and 120 min during an OGTT. Metabolite profiles from 30 obese subjects as independent samples were detected in order to validate the change of metabolites. There were the decreased levels of fatty acid, amino acids and biogenic amines after OGTT in obesity. At 120 min, percent change of 20 metabolites in obesity has statistical significance when comparing with the controls. The obese parameters was positively associated with changes in arginine and histidine (P < 0.05) and the postprandial change in palmitic acid (PA), branched-chain amino acids (BCAAs) and phenylalanine between 1 and 120 min were positively associated with fasting insulin and HOMA-IR (all P < 0.05) in the obese group. The postprandial metabolite of PA and BCAAs may play important role in the development and onset of insulin resistance in obesity. Our findings offer new insights in the complex physiological regulation of the metabolism during an OGTT in obesity.

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1. Introduction

Obesity, which has reached epidemic proportions, has become a priority in public health policies [1]. At present, 1.5 billion adults 20 years and older are overweight, and nearly 500 million of them are obese [2]. Obesity is closely associated with disorders of glucose and lipid metabolism which lead to insulin resistance and diabetes [3]. Therefore, better tools are needed to monitor the disease. With the development of many high-throughput measurement...
technologies, metabolomics have been used to investigate biomarkers of obesity.

Metabolomics, which is the study of complex metabolite profiles in biological samples, may provide a systems approach to understand the global metabolic regulation in an organism in relation to pathology [4]. Recently, there has been interest in applying metabolomics to examine alterations in the metabolic profile of obese subjects. These studies have provided strong evidence to suggest that alterations in the amino acid and lipid profiles are associated with obesity [5,6]. In those studies, glycerophosphatidylcholine, fatty acids, glycine and glutamine were found to be important biomarkers in the diagnosis of obesity. Moreover, Huffman et al. reported that fatty acids and neutral amino acids were independently associated with insulin resistance (IR) in obesity [7]. These findings suggested that metabolic alterations occurred in obesity, and that fatty acids and amino acids are closely related to IR in obesity based on metabolomics. However, these studies were performed in the fasting state [8,9], and the postprandial changes in metabolism could also contribute to the physiological function of the body. Therefore, it is necessary to investigate the potential effects of postprandial metabolic changes in fatty acids and amino acids in obese subjects.

Time-dependent variations in metabolic responses to the postprandial state are of significant importance in human health. The oral glucose tolerance test (OGTT), consisting of a standardized meal of pure carbohydrates, has been used to investigate these time-dependent variations. Numerous human studies have used the OGTT to investigate metabolic responses to this carbohydrate challenge (based on metabolomics [10,11]. Thus, in order to investigate metabolic changes in the physiological response during an OGTT in young obese and non-obese subjects, we analyzed the serum fatty acids, amino acids and biogenic amines profiles using a gas chromatography–mass spectrometry (GC-MS) and ultra-high performance liquid chromatography–triple quadrupole mass spectrometry (UPLC–TQ–MS) targeted metabolomics approach. We aimed to determine the metabolic changes influenced by this metabolic carbohydrate challenge and explore the association between these profiles and IR, thereby opening new perspectives in the study of the physiological reaction of obese subjects to glucose ingestion.

2. Methods

2.1. Subjects

The study was approved by the Ethics Committee of Harbin Medical University. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

2.2. Metabolic change in college students (MCS)

Subjects were young college students aged 18–23 years. 15 Lean [BMI (kg/m²) >18.5 and <23] and 15 obese (BMI > 27.5) healthy young men (Table S1) were recruited from Harbin Medical University in Harbin City via posters on campus, according to the criteria of the International Obesity Task Force [12] for Asians. The weight of all subjects was stable (<2.5 kg change over the past 3 months), and no medications likely to confound the study outcomes were taken by the subjects.

2.3. Metabolic change in validation study (MVS)

Thirty obese subjects aged 40–55 years (BMI, 33.87 ± 3.15) were recruited from the Hexing district in Harbin city of Heilongjiang in northern China via posters in the district. None of the subjects had diabetes mellitus, hyperlipidemia, hypertension or prior cardiovascular disease.

Anthropometric and biochemical measurements were shown in the Supplemental method (Method S1).

3. Serum fatty acids and amino acid profile analysis

Sample preparation for the serum free fatty acids, amino acids and biogenic amines was showed in the Supporting method (Method S1).

3.1. UPLC–TQ–MS analysis

UPLC–TQ–MS analysis was performed using a Waters ACQUITY UPLC system (Waters Corporation, Milford, MA, USA) coupled to a Waters Xevo TQD Mass Spectrometer (Waters Corporation, Manchester, UK). A 2 μl aliquot of the sample solution was injected into an ACQUITY UPLC™ HILIC column (100 mm × 2.1 mm i.d., 1.7 μm; Waters Corporation, Milford, MA, USA). The conditions of UPLC and MS were described in the supporting information (Method S1). In addition, the validation of this targeted method was also showed the result S1.

3.2. GC–MS analysis

GC–MS analysis was performed using gas chromatography coupled to an ion-trap mass spectrometer (TRACE GC/PolarisQ MS, Thermo Finnigan, USA) according to our previous work [13]. Separation was performed on a J&W DB-WAX capillary column (30 m × 0.25 mm i.d., 0.25 μm film thickness).

4. Statistical analysis

All data were presented as means ± SD. Multivariate statistical analysis was performed using SIMCA-P 12.0 software (Umetrics, Umeå, Sweden). Principal component analysis (PCA) was used first in all samples to observe the general separation. Partial least-squares-discriminant analysis (PLS-DA) was used to discriminate metabolite patterns between the OGTT time points.

Statistical analysis was performed using SPSS 16.0 (SPSS Chicago, IL Inc, UAS). The time course of the postprandial glucose and insulin response was analyzed by 2-factor repeated-measures ANCOVA with group and time as main effects. Differences in the postprandial response between time periods and weight status were assessed via time × group interaction.
<table>
<thead>
<tr>
<th>Metabolites</th>
<th>Control (n = 15)</th>
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<tr>
<td></td>
<td>BMI (kg/m²)</td>
<td>WC (cm)</td>
<td>HC (cm)</td>
<td>Body fat (%)</td>
<td>Fat mass</td>
<td>Fasting glucose</td>
<td>Fasting insulin</td>
<td>2h-Glucose</td>
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<tr>
<td>Leucine</td>
<td>0.84 (0.016)</td>
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<tr>
<td>Arginine</td>
<td>0.67 (0.018)</td>
<td>0.92 (0.003)</td>
<td>0.75 (0.042)</td>
<td>0.857 (0.014)</td>
<td>0.82 (0.021)</td>
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<tr>
<td>Phenylalanine</td>
<td>0.78 (0.026)</td>
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<td>Tryptophan</td>
<td>0.77 (0.041)</td>
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<tr>
<td>Histidine</td>
<td>0.78 (0.041)</td>
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<tr>
<td>Asparagine</td>
<td>0.73 (0.048)</td>
<td>0.57 (0.041)</td>
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<tr>
<td>FFA16:0</td>
<td>0.61 (0.039)</td>
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<tr>
<td>Metabolites</td>
<td>Obesity (n = 15)</td>
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<tr>
<td>Leucine</td>
<td>0.86 (0.006)</td>
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<tr>
<td>Arginine</td>
<td>0.66 (0.038)</td>
<td>0.69 (0.020)</td>
<td>0.76 (0.034)</td>
<td>0.58 (0.043)</td>
<td>0.86 (0.013)</td>
<td>0.714 (0.004)</td>
<td>0.56 (0.038)</td>
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<tr>
<td>Isoleucine</td>
<td>0.905 (0.002)</td>
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<tr>
<td>Phenylalanine</td>
<td>0.738 (0.037)</td>
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<tr>
<td>Histidine</td>
<td>0.78 (0.021)</td>
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<tr>
<td>Lysine</td>
<td>0.64 (0.036)</td>
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<tr>
<td>γ-Aminobutyric acid</td>
<td>0.92 (0.001)</td>
<td>0.75 (0.031)</td>
<td>0.71 (0.047)</td>
<td>0.76 (0.028)</td>
<td>0.61 (0.039)</td>
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<tr>
<td>Asparagine</td>
<td>0.76 (0.028)</td>
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<td>FFA16:0</td>
<td>0.69 (0.028)</td>
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BMI, body mass index; WC, waist hip circumferences; HC, hip circumferences; HOMA-IR, homeostatic model of assessment-insulin resistance.
Data for metabolites-clinical parameter associations which did not achieve statistical significance are not included.
Data are presented as standardized correlation-coefficients (p-values). Standardized correlation-coefficients were computed from standard deviations with p-values <0.05.
interaction tests. The baseline data and the percent change in metabolites at different time points (30, 60, 90 and 120 min) after the OGTT were analyzed using Student’s paired t test. The area under the curve (AUC) was calculated using the trapezoidal rule to quantify overall response to OGTT, which reflected both the amount and duration of the response. In addition, Spearman correlation analysis was also performed for the whole group using the percent change in metabolites from fasting to the 2-h sample and clinical parameters.

5. Results

5.1. Clinical characteristics of the subjects in MCS study

There were no significant differences between the obese and the control groups with respect to age, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), total cholesterol (TC), and dietary intake (Table S1 and Fig. S1). When compared with the controls, significant differences in BMI, waist circumference (WC), hip circumference (HC), body fat, fat mass and HOMA-IR were observed in the obese group (Table S1, P < 0.05).

5.2. Glucose and insulin profiles in MCS study

All subjects in the MCS study had normal fasting glucose levels (<6.0 mmol/l) and normal postprandial glucose (<7.8 mmol/l) (Fig. 1A). Glucose and insulin profiles were significantly different between the obese and control groups during the OGTT. The glucose and insulin concentrations at 30, 60 and 90 min in the obese group were higher than those in the controls (Fig. 1A and B, P < 0.05). Significant effects of group, time, and an interaction of time × group on glucose (group, P = 0.028; time, P < 0.001; interaction, P = 0.034) and insulin (group, P < 0.001; time, P < 0.001; interaction, P < 0.001) were observed. At 0–120 min, the glucose and insulin AUCs were statistically higher in the obese group compared with the control group (P < 0.05, Fig. 1C and D).

5.3. Metabolic profiles in MCS study

5.3.1. The metabolic profiles at baseline

We performed serum fatty acids profiles using GC-MS, amino acids and biogenic amines profiles using UPLC–TQ–MS in MCS subjects. Fifty-seven metabolites in fasting serum were detected in all subjects (Table S6) including 14 FFAs, 14 EFAs

Fig. 1 – Mean (±SD) postprandial serum glucose (A), insulin concentrations (B), glucose AUC (C) and insulin AUC (D) over 120 min after the OGTT in control (n = 15) and obese (n = 15) subjects. Repeated-measures ANCOVA showed significant main effects of group, time and the interaction of time × group on glucose (group, P = 0.028; time, P < 0.001; interaction, P = 0.034) and insulin (group, P < 0.001; time, P < 0.001; interaction, P < 0.001). * P < 0.05, compared with the value at 0 min of OGTT in the same group; † P < 0.05, compared with the value of the healthy control at the same time point of OGTT.
and 29 amino acids and biogenic amines. The levels of 31 metabolites changed significantly in the obese group when compared to the control group (Fig. 2, P < 0.05). In the obese group, higher levels of fatty acids including nine FFAs and 11 EFAs were observed compared with those in the controls. Compared with the controls, eight amino acids and biogenic amines significantly increased (leucine, valine, isoleucine, phenylalanine, proline, alanine, creatine and asparagine, P < 0.05) and three metabolites, glutamine, glutamic acid and taurine, decreased (Fig. 2, P < 0.05).

We also analyzed the data using multivariate statistical analysis. A plot of the PCA scores from all samples showed a separation between the obese and the control groups (Fig. S2A). The results of PLS-DA (Fig. S2B) showed a distinct separation between the two groups. These results suggested that the obese and control groups showed different metabolic profiles.

5.3.2. The metabolic change of different times during an OGTT

To analyze the metabolic alterations in detail during the OGTT, PLS-DA was performed on the serum samples collected at 0, 30, 60, 90 and 120 min. A clear classification at different time points was observed in the PLS-DA score-scatter plot derived from data from the obese and control groups (Fig. S3).

Thus, the levels of metabolites changed systematically during the OGTT in both groups.

The fold-change and significance of the metabolite changes during the OGTT in the control and the obese groups are shown in Figs. 3 and 4, and Fig. S4. The number of significant metabolites increased from 0 min to 120 min in both groups. With regard to the change in metabolites at 120 min, the levels of 25 metabolites in the obese group and 21 metabolites in the control group were significantly affected by the OGTT. The levels of a number of metabolites (n = 22), represented primarily by FFAs and amino acids, decreased at 120 min compared with the fasting state, and the levels of only a few metabolites (n = 3) increased (Fig. 4). When compared with the controls, the percentage change in 20 metabolites including four FFAs and 16 amino acids and biogenic amines in the obese group were significantly different (Fig. 4).

5.3.3. Correlation between clinical parameters and percent change from 2-h minus fasting metabolite response to an OGTT

Clinical parameters, such as BMI, WC, HC, body fat, fat mass, fasting glucose, fasting insulin, 2 h-glucose and HOMA-IR, were associated with changes in metabolite levels (Table 1). In the control group, BMI, WC, HC, body fat, and fat mass were positively associated with changes in arginine (all P < 0.05).
Fasting glucose positively correlated with the change in phenylalanine \((r = 0.78, P < 0.05)\) and 2 h-glucose was positively associated with leucine and tryptophan \((r = 0.84 \text{ and } 0.77, \text{ respectively}, P < 0.05)\). Fasting insulin was positively correlated with histidine, asparagine and FFA (16:0) \((r = 0.78, 0.73 \text{ and } 0.57, \text{ respectively}, P < 0.05)\), while HOMA-IR was positively associated with leucine and tryptophan \((r = 0.75, 0.75 \text{ and } 0.74, \text{ respectively}, P < 0.05)\).

With regard to the obese group, obesity parameters were positively associated with changes in arginine, histidine and \(\gamma\)-aminobutyric acid \((P < 0.05)\). Increasing fasting glucose levels were positively associated with changes in the levels of histidine \((P = 0.004)\). Fasting insulin was positively associated with several metabolites in response to the OGTT: leucine, isoleucine, phenylalanine, lysine, asparagine and FFA (16:0) \((\text{all } P < 0.05)\). In addition, HOMA-IR was significantly correlated with the changes in several metabolites during the OGTT including leucine, isoleucine, phenylalanine, histidine, lysine and FFA (16:0) \((\text{all } P < 0.05)\) (Table S7).

5.4 Validation in the obesity population

To confirm these findings, we determined the fasting and 2-h OGTT sample profiles from an independent study. This group had a similar BMI to the MCS group, however, these individuals were approximately 22 years older. Of the 25 metabolites which showed significant changes \((P < 0.05)\) in the MCS group at the 2-h time point during the OGTT (Fig. 4), similar trends were seen in the MVS group. These metabolite changes were significantly replicated \((P < 0.05)\) and were shown in Fig. 5. Thus, we identified 25 serum metabolites exhibiting highly reproducible and robust responses to glucose ingestion in obese subjects.

6. Discussion

In this study, we characterized 57 metabolites during a standard 2-h OGTT in the obese and control group using a targeted metabolomics approach. The profiles of several metabolites differed between the obese and control groups, and three major groups of metabolites were detected: EFAs, FFAs, and amino acids and biogenic amines. A decline in lipids including 11 EFAs, TG, TC, HDL-c and LDL-c was observed in the control and obese groups (Figs. S1 and S4). However, there were no statistically significant differences in the changes in these lipids during the OGTT in the two groups. These findings were similar to those in another study in obese subjects, which reported a fall in TG after the OGTT [14], and adds support to the notion that decreases in postprandial TG, TC and HDL-c after the OGTT were observed in men with abdominal obesity [15]. The above finding suggested that although there was a decreased trend in EFA, TG, TC, HDL-c and LDL-c during the OGTT, glucose ingestion has little effect on these lipids.

Several EFAs including palmitic acid (PA, C16:0), palmitoleic acid (C16:1), linoleic acid (C18:2) and linolenic acid (C18:3) in both groups, showed significant reductions during the OGTT. We and others have previously reported a decrease in FFA
levels in insulin-sensitive and insulin-resistant subjects during the OGTT [16,17]. Furthermore, we found that fasting FFA was higher and a blunted decline was observed in the obese group compared with the control group, which was confirmed in the study by Leung et al. [14]. These results suggested that elevated fasting levels and a delayed decrease in FFAs during the OGTT are important characteristics of metabolic perturbations in obesity.

Fatty acids are bioactive molecules that participate in cell structure formation, energy storage, and signal transduction. There are two types of fatty acids in the body, FFA and EFA. In this study, we found that there was a significant change in FFA, but not EFA in the obese group. Blood FFA levels, especially saturated fatty acids such as PA, have a central role in the development of diabetes, leading to IR, impaired insulin signal pathways and destruction of β-cells [18,19]. The mechanisms involved include increased saturated fatty acids resulting in the accumulation of various lipids, and saturated fatty acids have been shown to exert lipotoxic effects such as the induction of apoptosis, inflammation, and endoplasmatic reticulum stress which are associated with metabolic diseases [20,21]. In the present study, an increased fasting level and a
blunted decline in PA were observed in the obese group, and the change in PA during the OGTT was negatively correlated with HOMA-IR. These results suggested that there was a trend in IR in young obese subjects, although the HOMR-IR was less than 1.7. Taken together, these findings reflected the deregulation of free fatty acid metabolism in obese subjects, and may be beneficial in research into the pathogenesis of IR in obesity.

Another class of metabolite detected in our targeted metabolomics study was the amino acids and biogenic amines. At baseline, significantly low levels of glutamine and glutamic acid were observed in the obese group. Oberbach et al. reported that blood glutamine significantly decreased in obese individuals compared with lean individuals [6], which is consistent with our results. Importantly, serum branched-chain amino acids (BCAAs, isoleucine, leucine, valine) and aromatic amino acids (phenylalanine) in the fasting state were significantly increased in the obese group compared with the controls (Fig. 1). Consistent with our results, it was reported that high levels of BCAAs were observed in obesity and fasting concentrations of branched-chain and aromatic amino acids were correlated with obesity and serum insulin levels [22,23]. BCAAs, are essential amino acids in humans, and play central roles in protein metabolism [24], improving glucose metabolism [25] and regulating leptin secretion during food intake [26]. Newgard et al. [27] recently demonstrated that BCAAs contributed to obesity-related comorbidities such as glucose intolerance and IR. Moreover, elevated levels of BCAAs were reported to be strongly associated with the future risk of diabetes [28]. Therefore, it is necessary to detect postprandial changes in BCAAs in obese subjects and explore the association between postprandial changes in BCAAs and IR.

Another important finding in our study was the less pronounced decrease in several amino acids, such as BCAAs, phenylalanine and arginine during the OGTT in both groups. Earlier reports showed a gradual decrease in the BCAAs, isoleucine and leucine, during the OGTT in healthy subjects [29], which is also in agreement with the results obtained in the control group in our study. Furthermore, blunted decreases in these amino acids were observed in the obese group when compared with the control group (Fig. 4, P < 0.05) and the postprandial changes in these amino acids were validated in our study using another obese group in which the age of the subjects was greater (Fig. 5). In agreement with these findings, the levels of phenylalanine, isoleucine and leucine after an OGTT were significantly decreased in the obese group based on the metabolomics study [30]. This blunted decrease may be due to already increased basal levels of these metabolites in obese subjects, which may not increase further in response to elevated glucose or insulin levels [31]. Recently, a cluster of obesity-related amino acid metabolites demonstrated an inverse relationship with IR. Newgard et al. [27] observed associations between BCAAs and IR, and Tai et al. [32] reported that IR was associated with leucine, isoleucine, and phenylalanine. Thus, we assessed the relationship between IR and the postprandial changes in amino acids. We found that there were positive associations between the postprandial changes in leucine, isoleucine, phenylalanine, lysine, fasting insulin and HOMA-IR (Table 1). Although the idea that BCAAs and several related amino acids are linearly related to HOMA-IR has been supported by some studies [27,32], few studies investigated the relationship between the postprandial changes in amino acids and HOMA-IR. Therefore, our results suggest that these postprandial changes in several amino acids, especially BCAAs, may shed new light on the metabolic dysregulation associated with IR in obesity.

It is worth mentioning that correlations between postprandial changes in histidine and arginine and obese indices (BMI, WC, HC, body fat, fat mass) were found in this study. These
results suggest that the postprandial changes in histidine and arginine may be used as biomarkers in young obese subjects. In our previous study, we reported a lower serum histidine and arginine in obese women [33]. Thus, histidine and arginine are closely related to obesity. Reports have indicated that histidine can suppress appetite and influence body weight through its conversion into neuronal histamine in the hypothalamus of female subjects [34]. A clinical trial found that arginine increased antioxidant capacity in obese humans [35]. Thus, it may be of interest to investigate the mechanism of the postprandial changes in histidine and arginine in obesity, which may be helpful in improving obesity.

There are a number of limitations in the present study. First, although our results have been validated in independent samples, the number of subjects studied was relatively small. Thus, care must be exercised in the application of our findings to larger populations. Second, the relevance of the changes in the metabolic profiles in the mechanism of obesity could not be explained. Third, the included subjects did not represent a random sample of the Chinese population, and thus caution is required in generalizing the results of this study in the entire Chinese population. Therefore, further studies in this research field are needed.

7. Conclusion

In conclusion, analysis of the kinetic changes in serum metabolomics in obese subjects induced by a single carbohydrate challenge revealed significant metabolic alterations in free fatty acids and amino acids. Elevated fasting levels and a delayed decrease in free fatty acids and amino acids during the OGTT are important characteristics of metabolic perturbations in obesity. The correlation between postprandial changes in PA and BCAAs with IR in obesity may facilitate our understanding of the function of PA and BCAAs in obesity. Our findings offer new insights into the complex physiological regulation of metabolism during the OGTT in obesity.

Conflict of interest statement

The authors declare that there is no duality of interest associated with this manuscript.

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Appendix A. Supporting information

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2015.01.014

References


