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Original Article

Changes in insulin resistance are related to liraglutide-induced HMW-Adiponectin increase in obese type 2 diabetes

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Abstract: Liraglutide treatment could improve insulin resistance, while the underlying mechanism is not completely understood. Adiponection is a key component in the interrelationship between adiposity and insulin resistance, while the high molecular weight (HMW) adiponectin is the main active form. In this study we tested the hypothesis that the reduction of insulin resistance was associated with increase plasma HMW adiponectin mediated by liraglutide. A total of 45 obese type 2 diabetic patients were included in the 12-week observational, self-controlled clinical study. They were subcutaneously injected with liraglutide once daily as an add-on therapy based on their previous oral antidiabetic agents except for thiazolidinediones (TZDs). HOMA2-IR was calculated with serum glucose and C-peptide values using the validated calculator to evaluate changes of insulin resistance. Serum HMW-adiponectin concentration was tested by commercial ELISA Kit quantitatively. HOMA2-IR was significantly reduced, from baseline of 3.17±1.15 to 2.39 (1.89). There were positive correlations between δ FBG, post-HOMA2-IR, δ weight and δ HOMA2-IR. And there were inverse correlations between pre-treatment HOMA2-IR, δ HMW-APN and δ HOMA2-IR. By stepwise multivariate regression analysis, δ HOMA2-IR was predicted by δ HMW-APN. Insulin resistance was significantly improved after 12-week liraglutide treatment. Increased plasma HMW-adiponectin may play an important role in liraglutide-induced insulin sensitivity improving in obese type 2 diabetic patients.

Keywords: HMW-adiponectin, insulin resistance, liraglutide, T2DM

Introduction

Obesity and Type 2 diabetes have a complex relationship; obesity is linked to insulin resistance (IR), the precursor to type 2 diabetes [1]. It has been shown that visceral fat deposits are more metabolically active than their subcutaneous homologues, being particularly involved in the development of diseases associated with obesity, such as the metabolic syndrome (MS), T2D and coronary artery disease (CAD) [2]. Besides its function as an energy reservoir, adipose tissue has been recognized as the largest endocrine organ, which plays important roles in regulating lipid and glucose metabolism via secreting numerous bioactive molecules, such as adiponectin [3-6] and several others factors [7]. Adiponectin is the most abundant peptide secreted by adipocytes. Previous studies demonstrated that plasma high molecular weight (HMW) adiponectin is the form of more activity, it has much more closer relationship with diseases such as insulin sensitivity than low molecular weight (LMW) and hexameric medium molecular weight (MMW) oligomers [8, 9]. And higher levels of HMW will be conducive to improve IR. Evidences showed that in obese individuals, changes in adiponectin are related to weight loss mediated by dietary, exercise or bariatric surgery, while there were contradictory

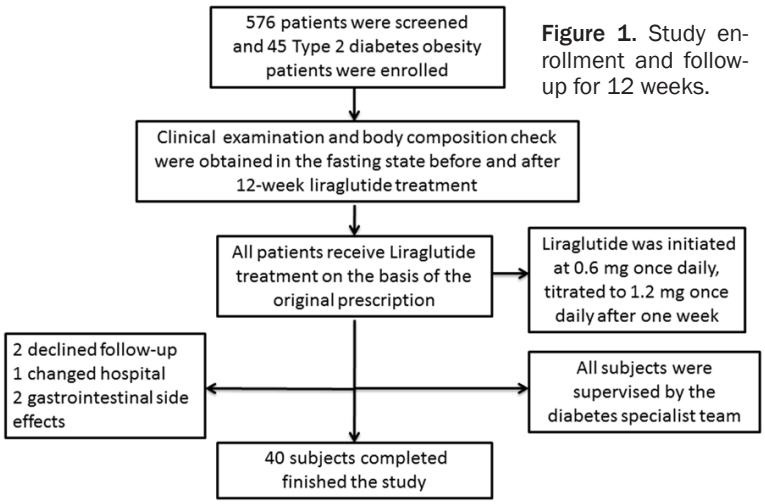

Figure 1. Study enrollment and follow-up for 12 weeks.

Table 1. The general information of included patients

Variable	Baseline (n = 40)
Sex (male/female)	21/19
Age (years)	50 (25-67)
Duration of diabetes (years)	7.25 (7.13)
HbA1c (%)	8.27±0.83
Body weight (kg)	91.05wei.87
BMI (kg/m^2)	30.24 (5.56)
Medications for diabetes	
Metformin (n, %)	40 (100%)
Sulphonylurea (n, %)	14 (35%)
Alpha-glucosidase inhibitor (n, %)	17 (42.5%)
Glinide (n, %)	15 (37.5%)

results existed [10, 11], visceral fat cannot be reduced by lifestyle intervention.

Furthermore, there are few relevant data about relationship between levels of circulating HMW adiponectin and weight loss induced by drugs such as liraglutide until now. Animal research results confirmed that GLP-1 can increase adiponectin level by pass iNKF cells. Our previous studies indicated that liraglutide could alleviate insulin resistance. The aim of this study was to investigate whether liraglutide-induced changes of IR were associated with changes of HMW-APN levels, and provided new insights into its underlying mechanism of improving insulin resistance.

Research design and methods

This was a self-controlled 12-week observational study. Subjects were recruited into the study after signing an informed consent upon admission to our institution. The study was approved by the Tianjin Medical University Ethics Committee Review Board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study population consisted of 45 T2D with obesity subjects. They were administrated subcutaneous liraglutide as add-on therapy. Patients were consecutively recruited by three diabetes specialists in the outpatient setting of the Metabolic Disease Hospital of Tianjin Medical University between September 2012 and August 2013. All patients were treated with the maximal tolerated dose of metformin before recruitment and they remained on the same mean dose throughout the study. The patient inclusion and exclusion criteria were as follows [12]: The inclusion criteria were: 1) known T2D with; 2) obesity (BMI ≥ 28 kg/m^2); 3) HbA1c 7.0~10%, and 4) at least 3 months treatment on a stable dose regime of maximal dose of metformin, or combined with either insulin, or any other oral anti-diabetes drugs except for TZDs. The key exclusion criteria were: 1) a history of coronary artery disease based upon a history of myocardial infarction, stable angina, congestive heart failure or unstable angina documented in physician notes or cardiac catheterization, 2) significant renal impairment (estimated creatinine clearance < 60 ml/min or serum creatinine > 150 μmol/l) or liver damage (serum alanine or aspartate aminotransferase three of more times the upper-normal range); 3) treatment within the last 3 months with pioglitazone, orlistat, any other drugs known to affect weight control, including glucocorticoids, or tamoxifen.

Clinical examination

All of the blood draws were obtained in the fasted state before and after 12-week liraglutide treatment. Blood glucose, HbA1c, and serum lipid profiles were measured. Methods were described detailed in our previous study [12]. Serum high weight molecular (HMW)-adiponectin was determined using the HMW-adiponectin enzyme linked immunosorbent assay

Table 2. Changes in body composition following 12-week liraglutide treatment

Variable	Pre-treatment (n = 40)	Post-treatment (n = 40)	Mean changes from baseline	*t/Z*	*p* value
Weight (kg)	91.05t (kg)	85.27t (kg)	-5.80 (-6.86, -4.74)*	10.977	0.000
BMI (kg/m^2)	30.24 (5.56)	29.39 (3.61)	-1.73 (-2.14, -1.56)	-5.443	0.000
e	275.82nal VA	235.22nal VA	-40.60 (-47.69, -33.50)	11.572	0.000
Abdominal SAT areas (cm^2)	208.58nal SA	187.41nal SA	-17.51 (-26.05, -16.29)	8.776	0.000
FBG (mmol/L)	9.25 (2.18)	6.82±0.70	-0.62 (-1.22, -0.72)	-5.512	0.000
P2BG (mmol/L)	13.07±2.30	8.67±0.91	-3.93 (-5.12, -3.68)	12.400	0.000
HbA1c (%)	8.27±0.83	7.14±0.56	-1.13 (-1.33, -0.92)	11.303	0.000

Normally distributed data are expressed as mean ± standard deviation and on-normally distributed data as median (Quartile Range). Paired t-tests were used to assess normally distributed data between individuals at pre- and post-treatment (pre-post) and are presented as mean differences with 95% confidence intervals. Wilcoxon Singed Ranks Tests were used to assess non-normally distribution data between individuals at pre- and post-treatment. *P* value < 0.05 was considered to be statistically-significant. BMI: body mass index. VAT: visceral adipose tissue. SAT: subcutaneous adipose tissue. BMI: body mass index. FBG: fasting blood glucose. P2BG: 2-hour postprandial blood glucose. HbA1c: glycosylated haemoglobin A1c.

(ELISA) (R & D Systems, USA), according to the manufacturer's instructions. Each sample was run in triplicates and the mean value was obtained by calculation using the standard curve method. Paired pre- and post-treatment samples were run on the same ELISA plate to minimize plate-related assay variation.

Anthropometry and body composition

Subjects underwent body measurement wearing only light clothing and without shoes in a fasting condition. Weight and height, waist and hip circumferences were measured. Anthropometric data were taken as the mean of two measurements. A single observer, who was not involved in the clinical care of the patients, made all of the above measurements. Total body weight, lean tissue mass, and fat mass were assessed by a low radiation DXA (GE Prodigy, WI USA) scan and single-slice abdominal CT (GE Healthcare, Milwaukee, WI, USA) was used to detect abdominal visceral and subcutaneous adipose tissue areas in fasting subjects before and after the 12-week liraglutide intervention period [12].

IR and homeostasis

Fasting serum C-peptide (FCP) was analyzed by enzyme linked immune sorbent assay (ELISA) methods. Serum glucose was determined by using the Hitachi 7070 automatic biochemical analyzer (Hitachi Ltd, Japan). HOMA2-IR was calculated with serum glucose and C-peptide values using the validated calculator (accessed at http://www.dtu.ox.ac.uk). C-peptide was used to avoid potential effects of fatty liver on insulin clearance in this study, which might distort HOMA2-IR calculations based on insulin.

Statistical analysis

Normally distributed data are expressed as mean ± SD and on-normally distributed data as median (Quartile Range). Data were tested for normality of distribution by the Kolmogorov-Smirnov test. Paired t-tests were used to assess normally distributed data between individuals at pre- and post-treatment (pre-post). Wilcoxon Singed Ranks Tests were used to assess non-normally distribution data between individuals at pre- and post-treatment. Spearman linear correlation test were performed to determine correlation coefficients between different parameters. Stepwise regression analysis was performed with potential confounders as the independent variables to determine if they may have had any significant effect on the changes in HOMA2-IR. The δ was used to demonstrate the change of values following liraglutide treatment with the calculation method of: δ = the value post-treatment minus the value pre-treatment). The statistical analyses were performed using SPSS windows version 17.0, and *P* value < 0.05 was considered as statistically significant.

Results

General characteristics of included participants

Between September 2012 and August 2013, a total of 45 subjects were enrolled in, and 40

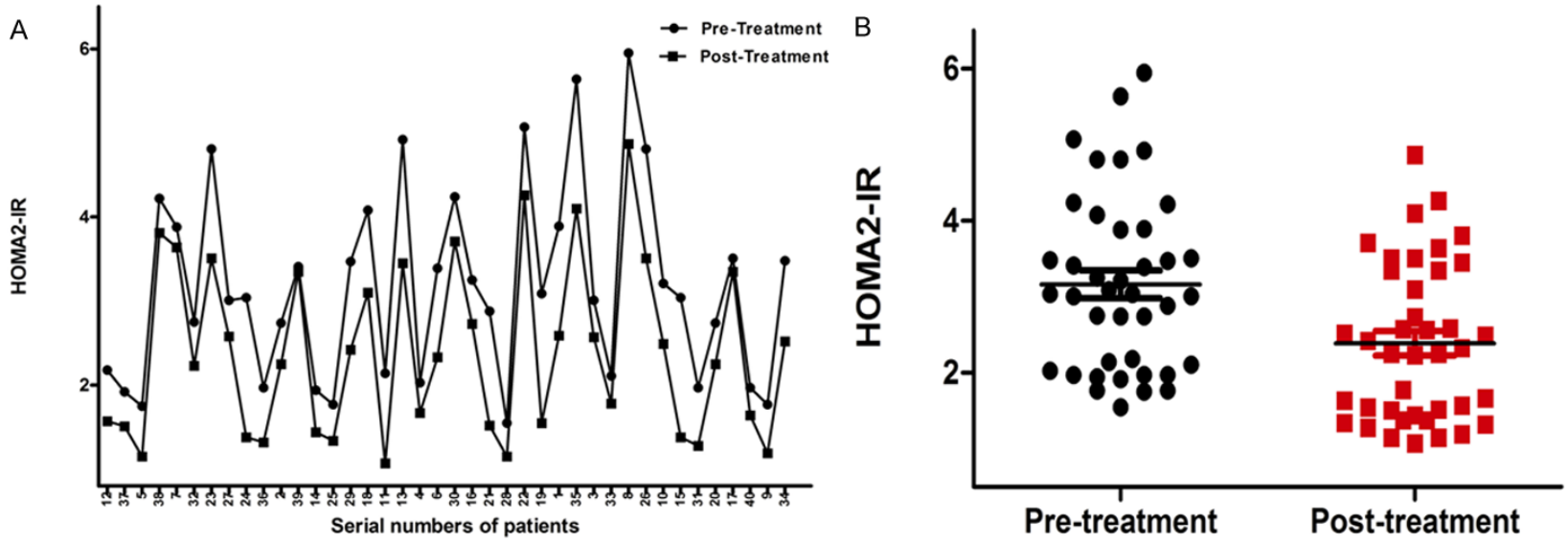

Figure 2. Changes in HOMA2-IR following 12-week liraglutide treatment. A: Data is presented according to the ascending order of absolute value changed of HOMA2-IR. B: Changes in the HOMA2-IR levels at pre-treatment and post-treatment.

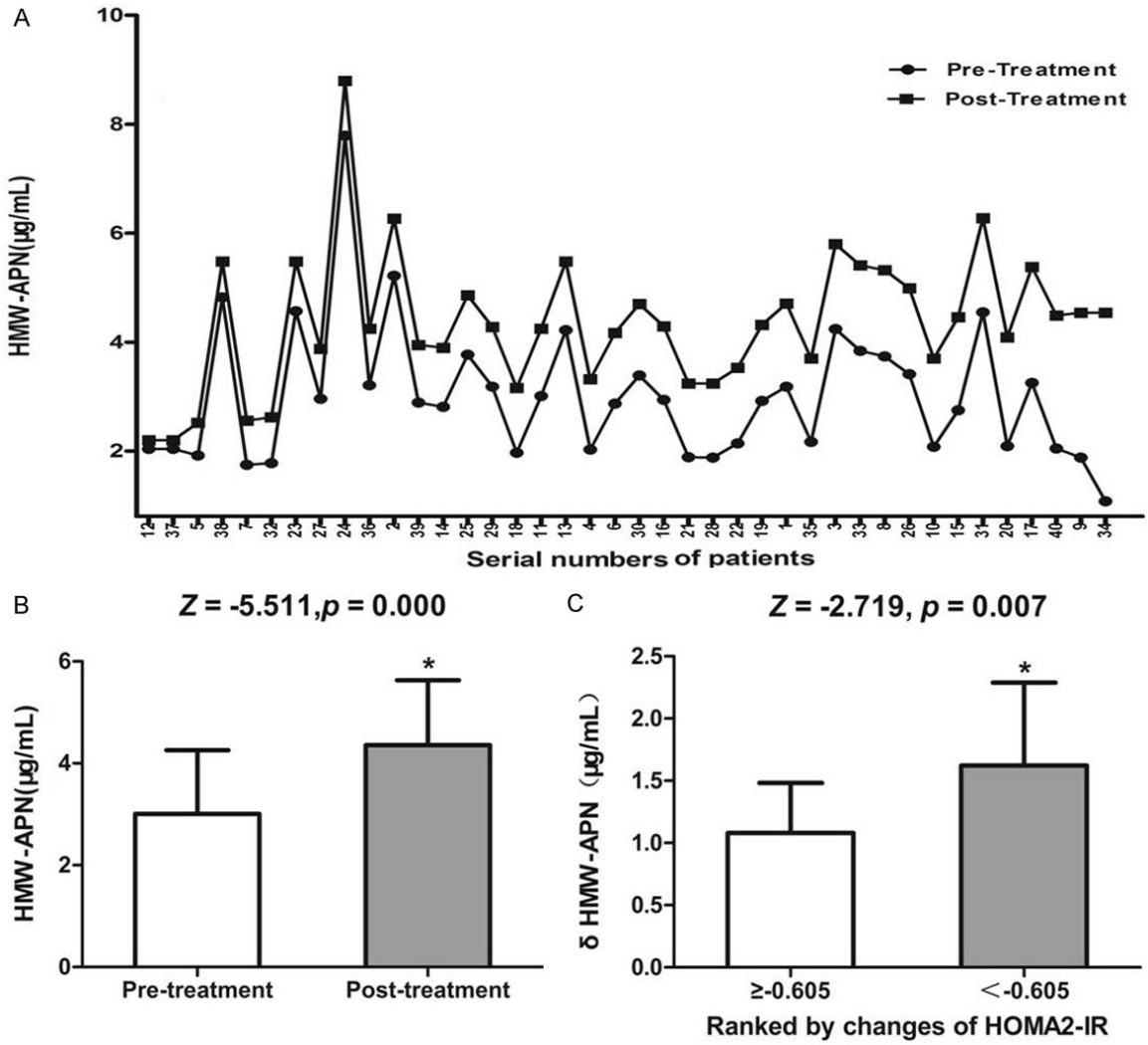

Figure 3. Changes in HMW-APN levels following 12-week liraglutide treatment. HMW-APN: high weight molecular adiponectin. A: Data is presented according to the ascending order of absolute value changed of HMW-APN. B: Changes in the HMW-APN levels at pre-treatment and post-treatment. C: Comparisons the increases in the HMW-APN levels within two subgroups stratified by median changes of HOMA2-IR (-0.605).

subjects completed the present study. 5 drop-outs after the experiment beginning, two declined follow-up, one changed hospital and two discontinued GLP-1 treatment due to gastrointestinal side effects (**Figure 1**). Detailed description of baseline characteristics of participants shown in our previous article [12]. The data indicated patients enrolled in this study had poor glycemic control and abdominal obesity. The mean HbA1c was 8.27±0.83%, and mean body mass index (BMI) was 30.24 (5.56) kg/m^2. The general information for included patients was shown in **Table 1**. And as reported previously, levels of FBG, P2BG, HbA1c, body weight, waist circumference and BMI were significantly reduced from baseline to post-treatment with liraglutide in all subjects. DXA and CT assessments showed significant reduction in both abdominal VAT and SAT areas and the relative mean reduction in VAT areas was greater than the relative SAT areas. Changes in glycemic control and body composition following 12-week treatment can be found in **Table 2**.

Changes in HOMA2-IR following 12-week liraglutide treatment

Results are presented in **Figure 2**, as we can see, the HOMA2-IR in all of the patients were decreased following 12-week liraglutide treatment (**Figure 2A**), and also the average changes in HOMA2-IR were significantly improved

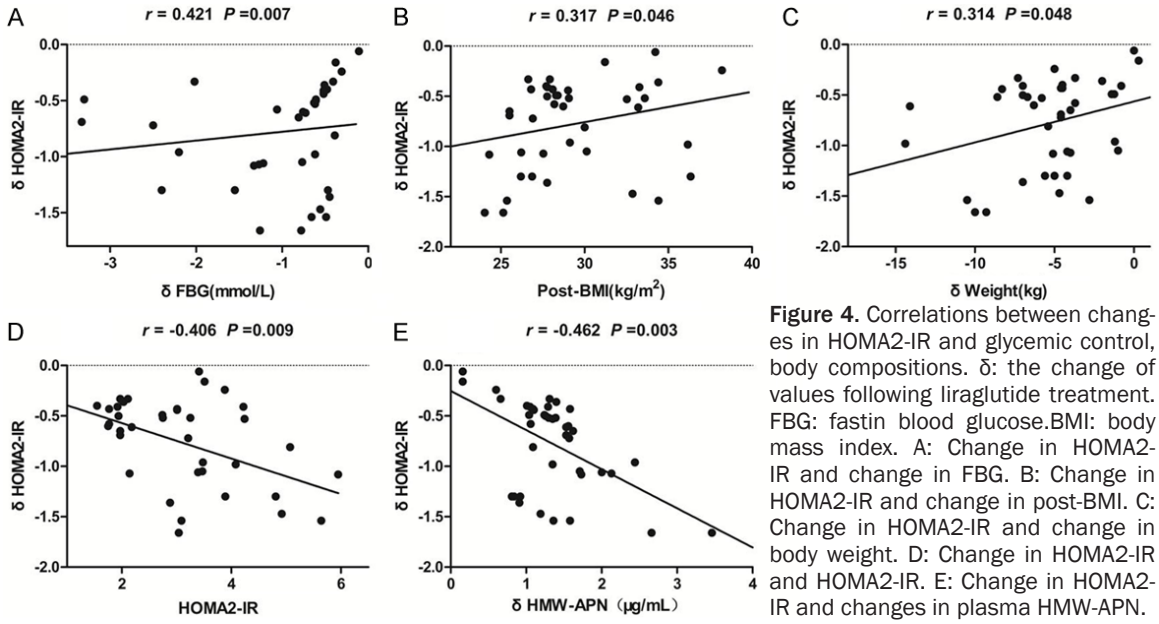

Figure 4. Correlations between changes in HOMA2-IR and glycemic control, body compositions. δ: the change of values following liraglutide treatment. FBG: fastin blood glucose.BMI: body mass index. A: Change in HOMA2-IR and change in FBG. B: Change in HOMA2-IR and change in post-BMI. C: Change in HOMA2-IR and change in body weight. D: Change in HOMA2-IR and HOMA2-IR. E: Change in HOMA2-IR and changes in plasma HMW-APN.

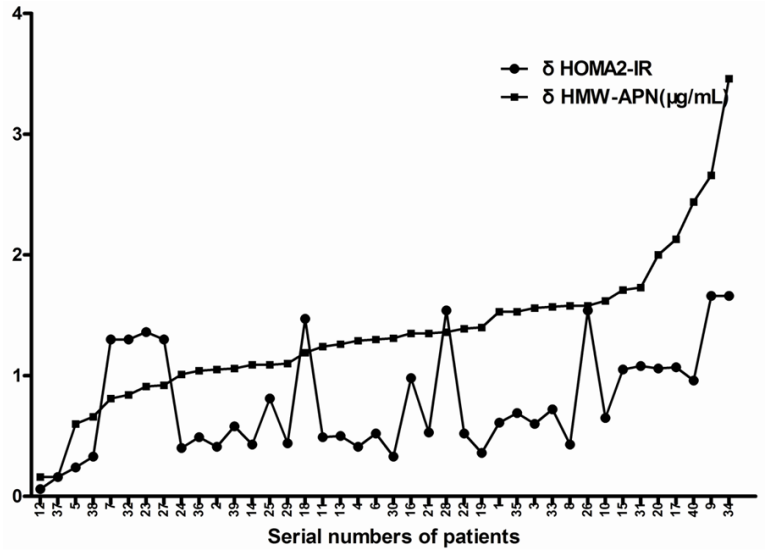

Figure 5. Changes in HOMA2-IR and change in HMW-APN. Data of changes in HMW-APN is presented according to the ascending order of absolute value changed of HOMA2-IR.

compared with baseline level (3.17±1.15 vs. 2.39 (1.89), Z = -5.512, P = 0.000) (**Figure 2B**).

Changes in HMW-APN following 12-week liraglutide treatment

As expected, 12-week treatment with liraglutide was associated with significant mean increased in HMW-adiponectin from baseline of 2.91 (1.62) μg/mL to 4.36±1.27 μg/mL (Z = -5.111, P = 0.000) (**Figure 3A**, **3B**). Furthermore, when we stratified patients into subgroups according to median of δ HOMA2-IR < -0.605 or ≥ -0.605 [patients with < -0.605 δ HOMA2-IR (n = 20) and patients with ≥ -0.605 δ HOMA2-IR (n = 20)], there was a significant increase in HMW-APN levels in patients who had more improvement of HOMA2-IR than 0.605 (1.17 (0.32) μg/mL vs. 1.62±0.67 μg/mL, (Z = -2.71, P = 0.007, **Figure 3C**).

Relationships between changes in glycemic control, body compositions and changes in HOMA2-IR

As hypothesized, glycemic control was improved following 12-week liraglutide treatment. And there were positive correlations between δ FBG and δ HOMA2-IR (r = 0.421, P = 0.007) (**Figure 4A**). There was positive correlations between post-BMI and δ weight (r = 0.317 and 0.314, P = 0.046 and 0.048, respectively, **Figure 4B** and **4C**). And there were inverse correlations between changes in HOMA2-IR and pre-treatment HOMA2-IR (r = -0.406, P = 0.009, **Figure 4D**). And there was negative correlation between δ HOMA2-IR and δ HMW-APN (r = -0.462, P = 0.003, **Figure 4E**). Furthermore, we

Table 3. Variables included in the correlation test

Independent variable	n = 40	Spearman's correlation coefficient	*p* value
Age (year)	50 (10.25)	-0.171	0.291
Duration of diabetes (years)	7.25 (7.13)	0.280	0.080
Pre-HbA1c (%)	8.27±0.83	0.026	0.873
Post-HbA1c (%)	7.14±0.56	0.076	0.640
δ HbA1c (%)	-1.13±0.63	0.044	0.787
Pre-FBG (mmol/L)	9.25 (2.18)	-0.034	0.837
Post-FBG (mmol/L)	6.82±0.70	0.185	0.254
δ FBG (mmol/L)	-0.62±0.79	0.421	0.007
Pre-P2BG (mmol/L)	13.07±2.30	0.094	0.564
e	8.67±0.91	0.258	0.108
δ P2BG (mmol/L)	-3.93±2.24	-0.032	0.842
Pre-Weight (kg)	91.05 Weight	0.213	0.186
Post-Weight (kg)	85.27 Weight	0.299	0.061
δ Weight (kg)	-5.80h1.22	0.314	0.048
Pre-BMI (kg/m^2)	30.24 (5.56)	0.229	0.154
e	29.39 (3.61)	0.317	0.046
δ BMI (kg/m^2)	-1.73 (4.07	0.240	0.135
Pre-VAT areas (cm^2)	275.82T area	0.031	0.849
Post-VAT areas (cm^2)	235.22AT area	0.151	0.353
δ VAT areas (cm^2)	-40.60 r22.19	0.268	0.095
Pre-SAT areas (cm^2)	208.58T area	0.125	0.441
Post-SAT areas (cm^2)	187.41AT area	0.104	0.523
δ SAT areas (cm^2)	-17.51 r15.26	-0.074	0.651
Pre-HMW-APN (μg/mL)	3.01±1.25	0.250	0.120
Post-HMW-APN (μg/mL)	4.36±1.27	-0.059	0.717
δ-HMW-APN (μg/mL)	1.35±0.61	-0.462	0.003
Pre-HOMA2-IR	3.17±1.15	-0.406	0.009
Post-HOMA2-IR	2.39±1.03	-0.026	0.876

Variable entered was δ HMW-APN and HOMA2-IR (β were -0.411 and -0.190, P = 0.000), model constant is 0.381. As a whole, this model explained 51.3% of the variability of change in HOMA2-IR after treatment by 12-week liraglutide (F = 19.480, P = 0.000). Excluded variables were post-BMI, δ FBG and δ weight (*p* value were 0.823, 0.962 and 0.983 respectively).

showed data of changes in HMW-APN according to the ascending order of absolute value changed of HOMA2-IR, and the changes trend of both was consistency (**Figure 5**). Studies have confirmed circulating adiponectin is inversely related to body mass index (BMI) and fat accumulation, and its ability to control insulin sensitivity has been extensively characterized in relation to states of insulin resistance, obesity, type 2 diabetes mellitus and coronary heart disease. First, the results confirmed the changes trend of changed HMW-APN and absolute value changed of HOMA2-IR was consistency. Second, through observing changed HMW-APN, we want to offer some clinical data for predicting improve insulin resistance.

Stepwise regression analysis between change in HOMA2-IR and potential correlative parameters

By stepwise multivariate regression analysis, changes in HOMA2-IR were predicted by δ HMW-APN (β = -0.388, P = 0.000), model constant is -0.252. As a whole, this model explained 27.7% of the variability of change in HOMA2-IR after treatment by 12-week liraglutide (F = 14.555, P = 0.000), (**Table 3**).

Discussion

In this study we tested the hypothesis that the reduction of insulin resistance was associated with increased plasma HMW adiponectin mediated by liraglutide. We reported that plasma HMW adiponectin concentrations were significantly improved while HOMA2-IR was decreased at the end of the course. Most interestingly, we found that δ HMW-APN was an independent predictor of changes in HOMA2-IR in subjects who treated with liraglutide.

The etiology of IR is complicated, genetic and environmental factors are involved [13]. HOMA2-IR is a kind of simple, reliable, non-invasive assessment of insulin resistance used epidemiological and clinical tool for the estimation of insulin resistance, which has a good consistency with euglycemic-hyperinsulinemic clamp [14-16]. Previous researches have confirmed that glucose toxicity is one of the factors that induce IR [17], and there is negative correlation between IR and glycemic control, confirming our results in which there were positive correlations between δ HOMA2-IR and δ FBG (r = 0.421, P = 0.007). Mounting evidence indicated that obesity is an independent risk factor for type 2 diabetes [18, 19]. Weight control is an important part in the management of T2DM [20]. Obesity especially abdominal obesity characterized by abdominal visceral fat is associated

with increased IR. Prior studies by others have reported that changes of body composition mediated by exercise or lifestyle can reduce fat tissues and attenuate IR [21]. We have previously reported that body weight, waist circumference, total fat and lean mass, fat percentage, SAT and VAT areas were significantly reduced from baseline after 12-weeks liraglutide treatment in obese T2D patients [12]. In current study, further analysis showed that there was positive correlations between changes in HOMA2-IR and post-BMI ($r = 0.317$, $P = 0.046$) and δ weight ($r = 0.314$, $P = 0.048$), which means that the patients who got higher weight loss may get more benefits.

Adiponectin secreted by adipocytes is an insulin sensitizing adipocytokine, which play important roles in appetite regulation and cellular energy metabolism [8]. And they circulates as multiple isoforms, with high molecular weight (HMW) adiponectin associated with greatest insulin sensitivity. Prior studies by others had different results about relationship between adiponectin and weight loss-induced through different methods, for instance caloric restriction, exercise and gastric bypass surgery [22, 23]. Research of Madsen E.L et al. shown that > 10% weight loss is required to significantly increase adiponectin levels [24]. By measuring the different oligomers, results showed no change [23-25], selective increase of HMW and MMW adiponectin [10], or all multimeric forms increased after weight loss [11]. All of these discrepancies possibly due to different experiment design include participant, study duration, obesity categories under evaluation, and magnitude of lost weight. Adipokines have been scarcely studied with GLP-1 receptor analogs, but most have been with exenatide treatment. The results of a research application of Exendin-4 showed that it can directly induce adiponectin expression, while the levels of HMW adiponectin had not been tested [26]. A prospective study used liraglutide to observe the beneficial effects of liraglutide on adipocytokines, insulin sensitivity parameters and cardiovascular risk biomarkers in patients with Type 2 diabetes. Results showed that changes in adiponectin did not reach statistical significant after 14 weeks of treatment [27]. Our current study suggests that the levels of HMW adiponectin increased compared with baseline after 12-week liraglutide treatment. The mechanisms are unclear based on the current study results. A study shows that GLP-1 may directly induce adiponectin expression through protein kinase. A pathway and prevents inflammatory adipokine expression [26]. And the mechanisms need further research.

Based on our findings, we suggest that increases of HMW adiponectin followed liraglutide induced weight loss may appropriately decreased IR in obese T2D patients. It would seem that a much better understanding of the molecular basis for changes in NPs following the weight loss induced by liraglutide is needed in the future. Further studies should investigate long-term interaction between HMW adiponectin and insulin resistance in these patients and explore the possible mechanism.

Limitations

There were several limitations in the present study. A relative small sample size was involved and observational design without use of control subjects in this study. We used HOMA2-IR to assess IR, which is inferior to the euglycemic-hyperinsulinemic clamp method to assess IR. Furthermore, due to lack of funding, total adiponectin and other components of adiponectin were not assessed, this may limit our discussion.

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Disclosure of conflict of interest

None.

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