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Original Article

The lifestyle changes after initiating basal insulin in insulin naïve patients with type 2 diabetes: Results from the ORBIT study

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ABSTRACT

Objectives: To evaluate the changes in diet, physical activity level and smoking status in insulin naïve patients with type 2 diabetes uncontrolled by oral antidiabetic drugs (OADs) after initiating basal insulins (BIs) for 6 months.

Methods: Observational Registry of Basal Insulin Treatment (ORBIT) program is a 6-month, prospective study in China. Patients with type 2 diabetes uncontrolled on OADs (HbA1c $\geq 7\%$, 53 mmol/mol) and willing to initiate BI treatment were enrolled. Type and dose of BI were at the physician's discretion and patients' willingness. Interviews were conducted at baseline, month 3 and month 6. Daily diet consumption, frequency of physical activity and smoking status in past 7 days were collected. Patients who kept using BI during the 6 months were included for analysis.

Results: Totally, 12 353 patients were included. Compared with the proportions at baseline, the proportion of patients with staple food of 0.4kg/day and above declined by 3%-4% at 6th-month, whilst the proportion of patients with moderate consumption (0.3kg/day) increased by 9.3%. The proportion of patients with 0.4kg/day vegetables increased by 4.2% and those with 0.2kg/day declined by 3.4% at 6th-month. Proportion of patients with 0.2kg/day fruit and meat increased by 12.5% and 7.6% respectively at 6th-month. Also, at 6th-month, patients spent more days participating physical activities weekly (5.8 vs. 5.3days), and both proportion of patients with smoking (20.0% vs. 22.9%) and number of cigarettes smoked per day (14.7 vs. 17.4) declined.

Conclusions: Adding-on BIs therapy is associated with positive lifestyle change including healthier diet consumption, more physical activities and less smoking behaviours in patients with type 2 diabetes.

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Introduction

Type 2 diabetes mellitus is a major public health challenge in China. According to a recent study, the estimated prevalence of diabetes among a representative sample of Chinese adults was 11.6% [1]. Maintenance

of optimal glycaemic control requires successive up-titration of antidiabetic drug treatment, and insulin is necessary for the majority of patients due to a natural progressive decline in pancreatic beta-cell function. Diabetes guidelines in general recommend adding basal insulin (BI) to existing oral antidiabetic drugs (OADs) as the initial insulin regimen, and if necessary, bolus insulin will be combined with BI for

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managing patients with more severe postprandial hyperglycaemia [2-5]. In clinical practice, the most commonly used BIs are intermediate-acting NPH insulin and long-acting insulin analogues glargine and detemir. Randomised controlled trials (RCTs) have demonstrated the efficacy of these agents in glycaemic control [6]. After the initiation of insulin therapy, some patients may follow doctors' education and pay more attention to their way of lifestyle, while others may relax the management of their lifestyle for the concept that insulin can control glycaemic level well and they no need to manage their lifestyle anymore. In real word, how adding-on insulin therapy can impact the patients' lifestyle--positive or negative, and to what extent the impact is are still unclear. In addition, patients with type 2 diabetes have psychological resistances on Insulin initiation, not only in China but worldwide [7-9]. About 40%-70% of patients have psychological insulin resistances [10, 11]. These resistances include viewing it as the last resort, fear of injection and/or pain, fear of hypoglycaemia and/or weight gain, poor self-efficacy about the skills required to administer insulin, etc [12]. Given that the start of insulin therapy needs most of patients to conquer their psychological resistances, it is reasonable to assume that adding-on insulin therapy may trigger some changes in patients' lifestyle pattern, such as physical activity, dietary pattern and smoking behaviour.

Previous studies mainly focused on the effect of lifestyle interventions on glycaemic control [13-17]. To date, no research has studied the impact of adding on insulin therapy on subsequent lifestyle changes. Based on the Observational Registry of Basal Insulin Treatment (ORBIT) study, we evaluated the changes in diet, self-reported exercise frequency and smoking status in patients with type 2 diabetes after initiating BI for six months.

Research Design and Methods

Study design

ORBIT was a 6-month, multicentre, prospective, registry study conducted in China. Details on study design and baseline characteristics of study subjects have been reported previously¹⁸. For each participant, interviews were conducted face to face at the beginning of the study (0 months, visit 1), mid-term (3 months, visit 2) and at the end of the study (6 months, visit 3). No intervention was given to participants. At visit 1, BI (insulin glargine, insulin detemir or NPH insulin) was prescribed, with or without prandial insulin, at the physicians' discretion and patients' willingness. Concomitant use of OADs at the time of BI initiation could be adjusted. During follow up, there was no limitation on therapy adjustments for insulin or OADs. Titrations of insulin dose(s) and medication regimen changes were all made according to the provider's recommendation and the patient's willingness.

Demographic and clinical characteristics were collected at baseline. Status of lifestyle factors (dietary consumption, physical activity and smoking) and clinical outcomes (HbA1c level, fasting plasma glucose (FPG) level, hypoglycemia episode and body weight et al) were documented at baseline and 6-month.

Lifestyle factors measurement

Lifestyle factors in this study included the daily amount of food consumption, frequency of physical activity and smoking status. Types of food included staple food—cereals (such as rice, wheat), vegetables,

fruits and meat consumption. Daily intake amount of each type in past 7 days was collected. The amount is in the unit of kilogram(kg). The frequency of physical activity included days participating any form of physical activity (such as doing housework, non-sedentary jobs and physical exercise) over 30 minutes in past 7 days, and days participating specific physical exercise (such as swimming, running, cycling) in past 7 days. Smoking status meant days having smoking behaviour in past 7 days, and number of cigarettes smoked per day in past 7 days. The original questionnaire used for collecting food intake, physical activities and smoking status was showed in (Supplemental Table S1).

Statistical analyses

A total of 12 353 participants who continued using BI at baseline and visit 3 were included in the analysis, and descriptive statistics were used for the analyses. For each food type, proportions of patients with each intake level at baseline and 6-month, as well as the average amount change of each intake level from baseline to 6-month were demonstrated. Frequency of physical activity in past 7 days, percentage of participants smoking in past 7 days and number of cigarettes smoked per day at baseline and 6-month were described. In addition to observing the lifestyle factors' changes in total participants, we also performed a subgroup analysis at 6-month to compare the lifestyle changes between controlled (HbA1c <7.0) and uncontrolled patients (HbA1c ≥ 7.0).

Continuous variables are presented as mean ± SD values. Discrete variables are presented as n (%). To the categorical variables, their distribution among different groups were tested by chi-square test. To the continuous variables, independent sample t test was used to test the difference between two groups. Statistical analyses were performed by using SAS (Version 9.4, SAS Institute Inc., NC 27513-2414, USA).

Results

I Demographic and clinical outcomes

After 6-month follow-up, 12 353 patients who continued using BI from visit 1 to visit 3 were included for this study. The demographic and clinical characteristics at visit 1 and visit 3 were listed in (Table 1). After 6-month follow up, the HbA1c level decreased by 2.14%, from 9.51% to 7.37%, and 42.2% of patients reached the target of HbA1c <7%. The BMI increased very slightly from 24.71 kg/m² to 24.74 kg/m². The frequency of minor hypoglycemia increased from 1.6 episodes/patient-year to 2.1 episodes/patient-year, while severe hypoglycemia decreased slightly, from 0.05 to 0.03 episodes per patient per year.

II Proportion of patients in each intake level of different food types

The proportions of patients in each daily intake level of specific food types at baseline and 6-month were shown in Table 2 and Figure 1. The proportions of patients with higher (0.4kg and above) staple food intake per day at baseline decreased at visit 3 (decreased by 3.0%-3.6%), whilst the proportions of patients with moderate consumption (0.3kg) increased significantly from 44.09% to 53.36%. To the consumption of vegetables, the proportions of patients with daily intake level of 0.4kg and 0.5kg at baseline increased by 4.2% and 1.3% respectively. To the consumption of fruit, the proportions of patients with 0.2kg/day (increased by 12.5%) and 0.3kg/day (increased by 2.4%) had a significant increase at visit 3,

while other levels decreased variably. The proportion of patients with meat intake of 0.2kg/day increased by 7.63%, while the proportion of

patients with $\geq 0.3\text{kg/day}$ decreased from 6.68% to 2.86% at visit 3 (Table 1).

Table 1: Patient characteristics at baseline and clinical outcomes at 6-month

Characteristics / clinical outcomes	Baseline (v1)	6 months (v3)
Male, n (%)	6606 (53.46)	-
Age (years), mean $\pm$ SD	55.61 $\pm$ 10.28	-
Out-of-pocket for medication (%), mean $\pm$ SD	40.70 $\pm$ 26.78	-
Current residence of patients, n (%)		
Urban	8601 (69.60)	-
Rural	3757 (30.40)	-
Education, n (%)		
Primary school or illiterate	3103 (25.11)	-
Junior high school	3766 (30.47)	-
Senior high school	3230 (26.14)	-
Junior college	1371 (11.09)	-
Bachelor's degree or higher	888 (7.19)	-
Duration of diabetes (years), mean $\pm$ SD	6.67 $\pm$ 5.29	-
Numbers of complication [†] , n (%)		
0	7811 (63.21)	-
1	2606 (21.09)	-
2	1297 (10.50)	-
≥ 3	644 (5.21)	-
Level of hospital initiating BI therapy, n (%)		
Secondary	6483 (52.46)	-
Tertiary	5875 (47.54)	-
Type of BI, n (%)		
Glargine	8777 (71.02)	8902 (72.03)
Detemir	1688 (13.66)	1585 (12.83)
NPH	1893 (15.32)	1871 (15.14)
SMBG [‡] times (times/month), mean $\pm$ SD	5.29 $\pm$ 9.85	6.42 $\pm$ 7.82
0, n (%)	3988 (32.27)	1948 (15.76)
1-5, n (%)	5213 (42.18)	5518 (44.65)
6-10, n (%)	1570(12.70)	2750(22.25)
≥ 11 , n (%)	1587(12.84)	2142(17.33)
BI dose (IU/kg/d), mean $\pm$ SD	0.18 $\pm$ 0.07	0.21 $\pm$ 0.09
HbA1c (%), mean $\pm$ SD	9.51 $\pm$ 1.96	7.37 $\pm$ 1.34
<7, n (%)	0(0)	5191 (42.18)
7-9, n (%)	5909 (47.82)	5789 (47.04)
9-11, n (%)	3867 (31.30)	1083 (8.80)
≥ 11 , n (%)	2582 (20.89)	245 (1.99)
Hypoglycemia (episodes/patient year), mean $\pm$ SD		
Severe	0.05 $\pm$ 0.87	0.03 $\pm$ 0.55
Minor	1.59 $\pm$ 9.91	2.10 $\pm$ 13.03
BMI (kg/m ²), mean $\pm$ SD	24.71 $\pm$ 3.32	24.74 $\pm$ 3.16

[†]Diagnosed macro/micro-vascular complications including coronary heart disease, stroke, peripheral vascular disease, diabetic nephropathy, retinopathy, peripheral neuropathy and others.

[‡]SMBG: Self-monitoring of blood glucose

III Amount change of each intake level in different food types

Amount and amount change of daily food intake at 6-month were showed in (Table 3) and (Figure 2). To the staple food intake, patients with intake level of 0.1kg/day at baseline increased to 0.21kg/day at visit 3. The ones with intake level of 0.3kg/day remained stable, while the ones with intake level of 0.4, 0.5 and $>0.5\text{kg/day}$ decreased by 0.10kg, 0.11kg and 0.14kg respectively at visit 3. To the vegetable intake, patients with intake level of 0.1kg/day increased by 0.15kg at 6-month.

To the amount of fruit intake, patient with intake of 0.3kg/day and above level decreased significantly at visit 3. Compared to the consumption of other three food types, the amount of meat intake changed slightly at 6-month.

IV Physical activities and smoking status at baseline and 6-month

After 6-month follow-up, compared to the baseline level, patients had

more days participating any form of physical activity over 30 minutes in past 7 days (5.83 ± 2.08 vs. 5.36 ± 2.49), and had more days participating specific physical exercise (3.97 ± 2.88 vs. 3.22 ± 3.05). For smoking,

compared to the baseline, both percentage of people smoking in past 7 days (19.98% vs. 22.91%), and average number of cigarettes smoked per day declined (14.66 ± 9.53 vs. 17.38 ± 11.03) at 6-month.

Table 2: Proportions of each daily intake level in specific food type at baseline and 6-month

Daily intake level (kg/day)	Baseline	6-month	P-value
Staple food			
0.1	212 (1.72)	158 (1.28)	>0.05
0.2	1933 (15.65)	2044 (16.55)	<0.05
0.3	5447 (44.09)	6591 (53.36)	<0.01
0.4	3131 (25.35)	2744 (22.21)	<0.05
0.5	1127 (9.12)	681 (5.51)	<0.01
>0.5	503 (4.07)	135 (1.09)	<0.01
Vegetables			
0.1	469 (3.80)	210 (1.70)	<0.05
0.2	2769 (22.42)	2346 (18.99)	<0.01
0.3	3416 (27.65)	3494 (28.28)	>0.05
0.4	2464 (19.95)	2982 (24.14)	<0.01
0.5	1822 (14.75)	1976 (16.00)	<0.05
>0.5	1413 (11.44)	1345 (10.89)	>0.05
Fruit			
0.1	4969 (40.23)	3341 (27.05)	<0.01
0.2	4816 (38.99)	6355 (51.44)	<0.01
0.3	1935 (15.66)	2229 (18.04)	<0.05
0.4	471 (3.81)	360 (2.91)	<0.05
0.5	76 (0.62)	32 (0.26)	<0.05
>0.5	86 (0.70)	36 (0.29)	<0.05
Meat			
0.1	2525 (20.44)	2354 (19.06)	>0.05
0.2	6188 (50.09)	7130 (57.72)	<0.01
0.3	2815 (22.79)	2516 (20.37)	<0.05
>0.3	825 (6.68)	353 (2.86)	<0.01

Data were shown in n (%).

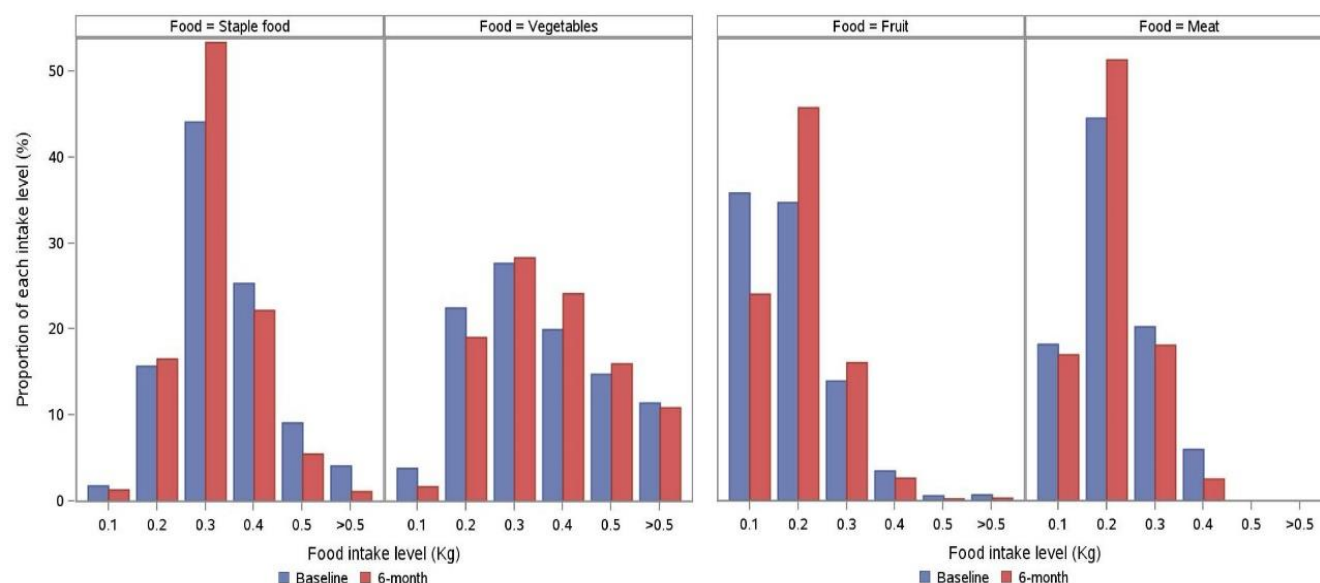


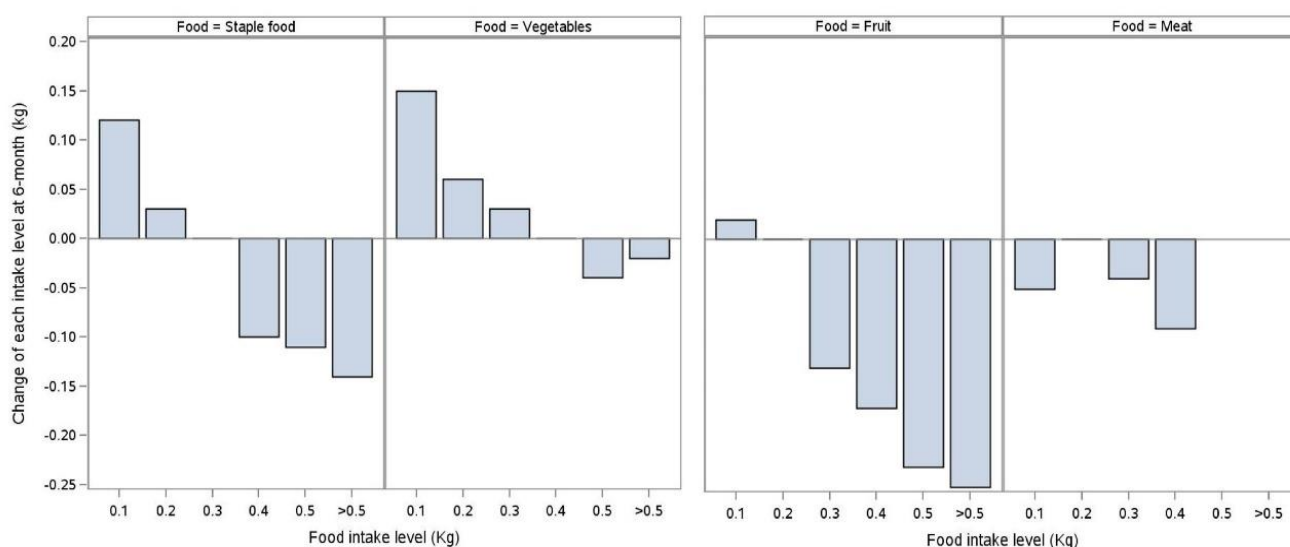
Figure 1: Proportion of each daily intake level in specific food types at baseline and 6-month

Table 3: Amount of daily diet intake at visit 3 and the intake change from baseline to visit 3

Amount of diet intake at baseline (kg)	Amount of diet intake at 6-month (g)	Chang of intake amount (g)*	P-value
Staple food ‡			
0.1	0.21 ± 0.09	0.12 ± 0.09	<0.05
0.2	0.21 ± 0.06	0.03 ± 0.05	>0.05
0.3	0.27 ± 0.05	0	>0.05
0.4	0.30 ± 0.07	-0.10 ± 0.06	<0.05
0.5	0.39 ± 0.08	-0.11 ± 0.08	<0.05
>0.5	0.36 ± 0.09	-0.14 ± 0.09	<0.05
Vegetables			
0.1	0.25 ± 0.12	0.15 ± 0.11	<0.05
0.2	0.26 ± 0.09	0.06 ± 0.09	>0.05
0.3	0.33 ± 0.09	0.03 ± 0.08	>0.05
0.4	0.37 ± 0.08	0	>0.05
0.5	0.44 ± 0.08	-0.04 ± 0.08	>0.05
>0.5	0.48 ± 0.09	-0.02 ± 0.09	>0.05
Fruit			
0.1	0.12 ± 0.06	0.02 ± 0.06	>0.05
0.2	0.20 ± 0.05	0.00	>0.05
0.3	0.17 ± 0.07	-0.13 ± 0.06	<0.05
0.4	0.23 ± 1.00	-0.17 ± 0.09	<0.05
0.5	0.27 ± 0.12	-0.23 ± 0.12	<0.01
>0.5	0.21 ± 0.14	-0.25 ± 0.14	<0.01
Meat			
0.1	0.05 ± 0.03	-0.05 ± 0.03	>0.05
0.2	0.18 ± 0.03	0.00	>0.05
0.3	0.26 ± 0.05	-0.04 ± 0.06	>0.05
>0.3	0.21 ± 0.07	-0.09 ± 0.07	>0.05

Data were shown in mean+ standard deviation (SD).

* Change of intake amount was calculated by using the amount at visit 3 minus the amount at baseline.

**Figure 2:** Amount change of each baseline daily intake level at 6-month

V Changes of lifestyle factors in controlled and uncontrolled patients

The change of lifestyle factors in controlled and uncontrolled patients were listed in (Table 4). Compared to the uncontrolled ones, patients with HbA1c <7.0 at visit 3 had more reduction in consumption staple food of 0.5kg/day at baseline. No significant differences were observed

among the changes in vegetable, fruit and meat consumption between the two groups ($p>0.05$). Patients with HbA1c <7.0 participated more physical activity at visit 3 (0.53 days vs. 0.42 days for any form and 0.86 days vs. 0.67 days for special physical exercise, $p<0.001$) and had larger reduction in percentage of smoking (-3.30% vs. -2.66%, $p<0.001$) and daily number of cigarettes used (-3.30 vs. -2.30, $p<0.001$).

Table 4: The change of lifestyle factors from baseline to 6-month in controlled and uncontrolled patients*

	HbA1c <7.0	HbA1c ≥7.0	P-value
Change of daily intake amount (kg) in past 7 days (Visit 3-Visit 1) [†]			
Staple food			
0.1	0.10 ± 0.10	0.15 ± 0.08	0.0116
0.2	0.03 ± 0.07	0.03 ± 0.06	0.9177
0.3	0	0	0.5432
0.4	-0.05 ± 0.06	-0.04 ± 0.06	0.0584
0.5	-0.09 ± 0.08	-0.09 ± 0.08	0.6229
>0.5	-0.15 ± 0.09	-0.10 ± 0.06	0.0275
Vegetables			
0.1	0.13 ± 0.11	0.15 ± 0.12	0.2111
0.2	0.06 ± 0.09	0.06 ± 0.09	0.2767
0.3	0.03 ± 0.07	0.03 ± 0.09	0.1763
0.4	0	-0	0.7453
0.5	-0.03 ± 0.08	-0.04 ± 0.08	0.2103
>0.5	-0.06 ± 0.08	-0.07 ± 0.09	0.5886
Fruit			
0.1	0.03 ± 0.05	0.04 ± 0.05	0.0630
0.2	0.01 ± 0.05	0.01 ± 0.05	0.7510
0.3	-0.14 ± 0.06	-0.13 ± 0.06	0.6254
0.4	-0.23 ± 0.09	-0.21 ± 0.10	0.4458
0.5	-0.29 ± 0.12	-0.26 ± 0.13	0.3386
>0.5	-0.23 ± 0.16	-0.25 ± 0.13	0.7236
Meat			
0.1	0.03 ± 0.03	0.03 ± 0.03	0.9087
0.2	0	0	0.1941
0.3	-0.04 ± 0.05	-0.04 ± 0.05	0.2309
>0.3	-0.09 ± 0.06	-0.09 ± 0.06	0.1041
Days participating physical activity in past 7 days (Visit 3-Visit 1)			
Any form of physical activity over 30 minutes	0.53 ± 2.11	0.42 ± 2.14	0.0005
Specific physical exercise	0.86 ± 2.53	0.67 ± 2.69	<.0001
Smoking (Visit 3-Visit 1)			
Change in proportion with smoking (%)	-3.30	-2.26	<.0001
Change in No. of average cigarettes per day	-3.30 ± 10.10	-2.30 ± 10.40	0.0002

*Changes of lifestyle factors were calculated by using the levels at visit 3 minus the levels at baseline.

[†]Diet consumption means the average daily consumption in past 7 days.

Discussions

Based on the assumption that psychological resistances pre-Insulin initiation may lead to lifestyle changes as a response after initiating insulin, our study indicated that after initiating BIs for six months, proportion of patients with moderate (0.3 kg) intake level of staple food increased, whilst higher (0.4kg and above) and low (0.1kg) intake levels declined. Compared with baseline, the overall amount of daily vegetable intake improved while the overall daily consumption of fruit dropped. Patients spent more days participating physical activities, and both proportion of patients with smoking and number of cigarettes smoked per day declined at 6-month. These lifestyle changes after initiating BI definitely will in return benefit to glycaemic control [19].

Food intake and physical activity levels are critical to type 2 diabetes, for decades, they have been considered as cornerstones of diabetes management, along with medication [20]. Staple food in this study indicates cereals—such as rice, wheat (flour-made food including steam bread, noodles, and fried bread stick, etc.), corn (maize), etc.—make up

a major part of most people's daily diets. These kinds of food are viewed as food with high glycaemic index (GI) [21, 22]. One literature review included 11 RCT studies, compared low GI or low glycemic load diet with higher GI diet, for subjects with type 2 diabetes without optimal control of glycaemia, found that low GI diet was associated with improved glycemic control [23]. Patients in ORBIT study with higher staple food intake (0.4kg and above) had a significant decline in month 6. This positive change implies that adding-on BIs therapy might trigger patients to reduce their high GI staple food intake, which may benefit the glycaemic control in return.

Two systematic reviews have indicated that consumption of fruit and vegetables provided no protection from type 2 diabetes [24, 25]. One of the review including 5 prospective cohort studies (167,128 participants and 4,858 incident cases of type 2 diabetes), with a mean follow-up period of 13 years, found that the relative risk (RR) and 95% confidence interval (95%CI) of type 2 diabetes for consumption of fruits and vegetables were 1.01 (0.88-1.15) and 0.97 (0.86-1.10) respectively [24]. Another review showed the RR (95%CI) were 0.96 (0.88-1.04) and 1.04

(0.94-1.15) respectively [25]. However, the conclusion is not sealed, a recent meta-analysis of prospective cohort studies including 24,013 cases of type 2 diabetes and 434,342 participants in the meta-analysis, found that the RR (95%CI) of type 2 diabetes for an increase of 1 serving fruit consumed/day was 0.93 (0.88-0.99), and for an increase of 0.2 serving green leafy vegetables consumed/day was 0.87 (0.81-0.93) [26]. In our analysis, we found the intake amount of daily vegetable consumption improved while the amount of fruit dropped at 6-month. This indicates that the starting BIs therapy might promote people to eat more vegetables while fewer fruits. This may be due to most of the routine fruits are with high GI (e.g., watermelon, grapes), patients tend to avoid eating them after initiating BIs.

Frequent meat consumption has been shown to increase the risk of developing type 2 diabetes. A meta-analysis of 12 cohort studies found that the RR of diabetes comparing high to low intake was 1.17 for total meat (95% CI: 0.92-1.48) and 1.21 for red meat (95% CI: 1.07-1.38) [27]. At month 6, proportions of patients with >0.3kg of daily meat consumption declined and 0.2kg level increased, indicating a positive change in meat consumption.

Apart from diet, another critical lifestyle factor related to the effect of glycemic control is physical activity. Intensity and amount of physical activity are related to insulin sensitivity [28]. It is suggested that exercise can substitute pharmacological treatment in patients with prediabetes and type 2 diabetes, and glycaemic level could be reduced by 30-50% with regular to vigorous exercise [29, 30]. In ORBIT study, after adding on BIs, people tended to spend more time to do physical activities, this definitely would benefit their glycaemic control. Evidence has shown that cigarette smoking is an independent risk factor for type 2 diabetes [31-33]. After initiating BIs for six months, patients' proportion with smoking and daily number of cigarettes smoked declined, which implies adding on BIs therapy can promote people to improve their smoking behaviour.

This study has its strengths and limitations. To date, we found no study has evaluated the lifestyle change after starting basal insulin therapy. Substantial previous studies have focused on the effect of lifestyle interventions or lifestyle change combined with medication on glycaemic control [13-17]. To our knowledge, this is the first prospective study up to date to evaluate the impacts of adding-on BIs on lifestyle change in realistic clinical setting. Also, the large sample size enabled us to detect the differences powerfully. However, there are several limitations need to be acknowledged. First, the self-reported information of lifestyle factors might cause some recall bias. However, as a lifestyle is a habit and can be tracked, we suppose the collected information in past 7 days could reflect the real situation to a great extent. In addition, as an observational study without a control group (before-after comparison was used in this study), a causal effect between starting BIs and lifestyle changes still cannot be confirmed. It might be the case that those who accepted basal insulin therapy were also the ones willing to change their lifestyles. Thus, future studies with control group are needed to verify our findings.

In conclusion, our results imply adding-on basal insulin therapy is associated with positive lifestyle changes including healthier diet consumption, more physical activities and less smoking behaviours in patients with type 2 diabetes. Further studies (i.e., clinical trials with control arm) are needed to confirm the causal effect between them.

Author contributions

L.J., P.Z. and D. Zhu contributed to the study design and interpreted findings. D. Zhu contributed to data analysis, drafting of the manuscript and interpretation of findings. X.L., J.J. and H.Z. contributed to the data analysis, interpretation of findings, J.L. and W.J. contributed to the study design, site selection.

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Disclosure statement

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