Outcomes and safety of concomitant topiramate or metformin for antipsychotics-induced obesity: A randomized controlled trial

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Abstract

Background

Although some data exist describing the use of topiramate in patients with antipsychotic-induced obesity, direct comparision with metformin is limited. The purpose of this study was to explore the effectiveness and safety of concomitant topiramate on antipsychotic-induced obesity and compare with metformin.

Methods

62 stabilized outpatients with antipsychotic-induced obesity were randomized to 16-week treatment group of topiramate or metformin. The patients’ weight, body mass index (BMI), waist-hip ratio and side effects were assessed and compared. Intention-to-treat and completer analyses were performed. Meanwhile, Covariance analysis was conducted to control the impact of the significant difference in BMI when comparison between the two groups.

Results

Two groups had comparable characteristics though the difference in baseline BMI was significant. Intention-to-treat analyses: The random missing values were replaced using the last observation carried forward method when intention-to-treat analyses. Compared with the baseline, the weight, BMI and waist-hip ratio with topiramate markedly decreased at each follow-up, whereas, only waist-hip ratio with metformin significantly decreased at 4-week. Compared with metformin, only weight and BMI with topiramate significantly decreased at 4-week, and all weight, BMI and waist-hip ratio at week 8–16 also remarkably declined. Completer analyses: Compared with the baseline, the weight, BMI and waist-hip ratio with topiramate at week 4–16 markedly decreased, whereas, only waist-hip ratio with metformin significantly decreased at 4-week. Compared with metformin, all BMI with topiramate markedly decreased at week 4–16, moreover weigh and waist-hip ratio also notably lowered at 8-week. No significant differences in adverse events were found between the two groups.

Conclusions

Topiramate, similar to metformin in reducing obesity as previously reported, also significantly reduced body weight, BMI and waist-hip ratio in patients with antipsychotic-induced obesity and demonstrated well tolerance in psychiatric patients.

The trial was registered at http://www.chictr.org.cn, and the number was ChiCTR-IPR-17013122.

Introduction

Second-generation antipsychotics (SGAs) (except for clozapine) have been extensively used in patients with schizophrenia, affective disorder and other psychiatric disorders in the past three decades due to its little extrapyramidal symptoms. Whereas, previous researches have linked some patients exposure to
some SGAs to an increased risk for weight gain or obesity, hyperlipidemia, and impaired glucose metabolism, which has been a serious problem. Especially, weight gain or obesity induced by SGAs have been commonly reported and warranted significant concern, because they may significantly increase both the risk of cardiovascular disease and mortality from cardiovascular disease,\textsuperscript{1,2} moreover, the treatment of obesity caused by SGAs still remains a challenge to the clinician. So far, there is no consensus on the exact effective and safe drug of weight loss although many measures had been implemented to promote weight loss, which include dietary control, physical exercise, taking some antiobesity medications, and so on.\textsuperscript{3,4}

Apart from nutritional and behavioral interventions, switching to first generation antipsychotics or other SGAs, many pharmacologic medications have been utilized to reduce weight gain or obesity induced by SGAs or non-pharmacological obesity in the past. For example, sibutramine, reboxetine, bupropion, orlistat, liraglutide, fluoxetine, metformin, topiramate, and antagonism of the histamine 2 (H2) receptor, etc. were also reported to have significant effects on weight gain compared to placebo,\textsuperscript{5–8} whereas, some previous studies’ results were not consistent each other, even there are some conflicting reports.\textsuperscript{9}

Metformin, a biguanide drug approved for treatment of type 2 diabetes, has been extensively studied for use of weight gain in the absence of diabetes in typically developing children.\textsuperscript{10,11} In adults or pediatric patients or adolescents, metformin may prevent or reverse or significantly attenuate weight gain associated with atypical antipsychotics\textsuperscript{12–14} although some confound factors are difficult to be excluded, such as differences in patient population, lifestyle and dietary interventions. Meanwhile, metformin may induce the accumulation of metformin and the risk of lactic acidosis except for causing nausea and diarrhea, especially in patients with impairment of renal function.

Topiramate, a new antiepileptic drug, which is increasingly being used as a mood stabilizer in bipolar disorder, and does not cause parkinsonism, has also been used as adjuvant therapy for both the positive and negative symptoms of schizophrenia.\textsuperscript{15–17} And it holds some promise as an adjunctive therapy for both overweight and treatment of psychotic symptoms.\textsuperscript{5} Topiramate has the strongest mean weight loss compared with placebo, metformin, H2 receptor antagonists, and norepinephrine reuptake inhibitors in some reviews\textsuperscript{5, 8,18, 19} although it has some adverse events which are possibly uncommon. Whereas, the effect of topiramate on patients with obesity caused by SGAs varied in different studies, some of the studies were either smaller samples or lack of placebo-controlled trial, or reported as other researches’ additional results, and did not exactly infer the effects of topiramate on weight loss.\textsuperscript{20}

It is generally acknowledged that an ideal medication of weight loss in patients with mental disorders can reduce weight effectively already, also can stabilize original mental symptoms effectively, better yet, it can further prevent relapse of mental disease. In fact, the treatment of weight gain or obesity induced by antipsychotics remains a significant challenge to psychiatrists, because there is relatively little evidence of specificity for pharmacological therapies to antipsychotic-induced weight gain, moreover, there is no consensus on the exact effective and safe drug of weight loss until now. Although some studies have
evaluated the effects of topiramate or metformin on weight gain, they usually compared with the placebo, only one investigation with sibutramine.\textsuperscript{21}

Up to now, there is no research report on the direct comparison between topiramate with metformin on weight gain or obesity induced by SGAs in the real world. To better understand the effects and adverse events of topiramate on weight gain, or a stabilizing effect of topiramate on psychosis, this study was to explore the effects of concomitant topiramate or metformin on obesity caused by some second generation antipsychotics while keeping the patient's illness stable and maintaining the original antipsychotic medications.

**Methods**

**Study Design and Participants:**

This study was a 16-week, open design, randomized clinical trial, and all outpatients or inpatients with schizophrenia or affective disorder were Chinese Han population and from Huai’an No. 3 People's Hospital in a naturalistic clinical setting from September, 2012 to December, 2016.

Informed consent was obtained from patients or their legal guardians after enrollment. The protocol for the study was granted approval from the scientific and ethics committee of Huai’an No. 3 People's Hospital (Ethical Review No. HASYkjk 2012-003).

Patients included in this study were diagnosed with schizophrenia or affective disorder based on Diagnostic and Statistical Manual of Mental Disorders\textsuperscript{\textregistered} DSM-\textsuperscript{5} by reviewing clinic medical records. All outpatients or inpatients’ illness (n=2) were in a stable condition, and the age was from 15 to 55 years. Patients were not obese before taking antipsychotics and had been on antipsychotics for at least six months before enrollment, and currently met the diagnostic criteria for obesity, which was specified as a BMI over 25kg/m\textsuperscript{2} based on the Regional Office for the Western Pacific Region of WHO criteria.\textsuperscript{22}

Patients were excluded from the study if they had a history of intolerance or hypersensitivity to topiramate and metformin, or had a severe or unstable general medical illness, such as renal and liver function failure, or severe cardiovascular diseases. Patients who were pregnant and/or during lactation period were also not included.

70 cases of patients with schizophrenia or affective disorder with obesity induced by second-generation antipsychotics met with the inclusion criteria, 8 of them declined to participate the trial after the enrollment. Only 62 cases of obese outpatients (n=60) and inpatients (n=2) with schizophrenia or affective disorder in a stable condition of illness were randomly assigned to 16 weeks of concomitant topiramate or metformin treatment arm according to randomized table generated by online smart random A and B generator (A represents the topiramate group, B represents the metformin group). All patients continued to receive the original antipsychotic medications and community psychiatric care or did some light manual works after enrollment.
All assessments were done by investigators, and the patients’ indicators must be accurately measured although investigators had known the patients’ therapy allocation at each follow-up visit.

**Interventions**

All patients were given a screening questionnaire, which included previous diagnosis in clinic or during hospitalization, the use of antipsychotic medications and their demographic features. All patients and caregivers only received brief counseling and information regarding the patients’ dietary management and physical exercise after enrollment of the trial.

The dosage of each antipsychotic the patients previously used remained unchanged as much as possible during the trial unless psychotic symptoms exacerbated or severe adverse events emerged. The treatment would be discontinued if researcher decided that a patient’s response was not adequate or the patient asked to be withdrawn from the trial due to severe adverse events or illness exacerbation.

The initial treatment dosage of topiramate was 50mg twice daily, if tolerated, the maximum dose was 100-200mg twice daily after week 1, and the mean daily dose of topiramate was 190.63±57.41mg after 16-week treatment. The initial treatment dosage of metformin was 0.25g twice daily, if tolerated, the maximum daily dose of metformin was 1.5g after 1-week, and the mean daily dose of metformin was 0.67±0.22g after 16-week treatment. All patients received diet, drinking or exercise counseling, no other requirements were conducted.

All patients were required to be followed up every four weeks for at least 16-week after concomitant topiramate or metformin treatment. Patient's weight, height, waist and hip circumference (W-H ratio) were measured while dressed in light clothing without shoes on the same scale zeroed at each measurement and calculated by researcher at each follow-up visit. And blood routine, liver function and electrocardiogram examination were also conducted as possible as we can at each follow-up visit. Whereas, a few patients still cannot be followed up in time due to the bad weather condition or personal reasons. The status of the enrollment, the completed and withdrawn samples was shown below between the two groups. See figure 1.

**Outcome Measurements**

The primary outcome measures were weight, height, body mass index (BMI) and W-H ratio at each follow-up visit. The BMI was calculated as weight in kilograms divided by height in meters squared, and W-H ratio was calculated as waist circumference divided by hip circumference.

The secondary outcomes measures were the patient's liver function, blood routine, electrocardiogram, and other adverse events were also monitored after concomitant topiramate or metformin. Of course, the psychotic symptoms were also paid close attention to observe at each follow-up visit during the trial.

**Statistical Analysis**
The statistical analysis was carried out using SPSS 13.0 (SPSS Inc., Chicago, Illinois, USA). The categorical variables were tested using a $\chi^2$ test, the continuous variables were tested by means of a repeated measurement variance analysis before and after treatment in each group of concomitant topiramate or metformin, and independent samples t-test between the two groups.

All missing data at each follow-up visit were random missing data by randomized analyses, and the missing data at week 4-16 of follow-up visit were replaced using simple imputation (last observation carried forward method, LOCF) when intention-to-treat (ITT) analyses was performed. 23

An intention-to-treat and completer analyses were performed between the two groups because of higher loss rate of follow-up. Covariance analysis was conducted to control the impact of the significant difference in baseline body mass index (BMI) when compared the patients’ weight, BMI, waist-hip ratio at 4-16 weeks of follow-up visit between the two groups.

All statistical tests were two tailed. The values represented as mean ± standard deviation (SD) at each follow-up visit. P value<0.05 was considered statistically significant.

**Results**

62 cases of patients entered a 16-week of the trial between the two groups. Of 62 cases of patients with obesity, there were 32 cases of outpatients or inpatients into the topiramate group and 30 cases into the metformin group respectively (See figure 1).

**Comparison of patients’ demographic and clinical features at baseline between the two groups**

There were no statistically significant differences in gender, age, marital status, occupation, educational level, parents’ history of obesity, the diagnosis types of mental disorder, chlorpromazine (CPZ) equivalent daily dose of antipsychotics,24,25 types of antipsychotics and daily dosage of clozapine and olanzapine being used between the two groups. In addition, no remarkable differences were found in the type and the number of use of combined antipsychotics, affective stabilizers, antidepressants, chlorpromazine (CPZ) equivalent daily dosage of use of combined antipsychotics, and the number of outpatients and inpatients between the two groups. So the patients’ demographic, clinical characteristics and the factors that continued to influence weight gain during the trial were comparable and matched between the two groups. See table 1-2.

**ITT Analyses**

**The effects of concomitant topiramate or metformin on weight gain, BMI and W-H Ratio at each follow-up visit in each group or between groups before and after treatment.**

All missing data at each follow-up visit were randomized missing data by randomized analysis, and the missing data at each follow-up visit were replaced using the last observation carried forward method (LOCF) when ITT analyses was performed.
Compared with the baseline in each group, the body weight, BMI and most waist-hip ratio at each follow-up visit markedly decreased (all P value<0.001), only waist-hip ratio at week 4 of follow-up visit significantly decreased in the topiramate group (t=2.63, P<0.05), while no differences of weight loss, BMI and waist-hip reduction ratio were found at each follow-up visit compared with baseline in the metformin group. See figure 2.

Compared with the metformin group, only weight and BMI at week 4 of follow-up visit in the topiramate group significantly declined (t=4.38, P<0.05; t=9.28, p<0.01), but there was no difference in waist-hip ratio at 4-week of follow-up visit between the two groups. The reduction of weight, BMI and waist-hip ratio at 8, 12 and 16-week of follow-up visit in the topiramate group were all remarkably more than that in the metformin group (P<0.05, or P<0.001). See figure 2.

**Completer analyses**

**Effects of concomitant topiramate or metformin on weight, BMI and WHR reduction in the outpatients who completed the trial at each follow-up visit in each group or between the two groups before and after concomitant treatment.**

Figure 1 showed the status of completed this trial at each follow-up visit. Only 10 cases of patients in the topiramate group and 15 cases of patients in the metformin group at week 16 of follow-up visit were included in the completer analyses. The rate of lost to follow-up was similar at week 4-16 of follow-up visit between the two groups (all P>0.05) (See table 1).

**Compared with the baseline in each group,** Statistically significant reductions of weight, BMI and W-H ratio from week 4 to 16 of follow-up visit were found in the topiramate group (All P value<0.001). However, only statistically remarkable reduction of W-H ratio at week four of follow-up visit was found in the metformin group (P<0.05), there were no differences in weight loss and BMI reduction at week four of follow-up visit, and the differences in main measurements of three items at other follow-up visit were also not found in the metformin group. See figure 3 (A-C).

**Compared with the metformin group,** there was significant difference in reduction of BMI from week 4 to 16 of follow-up visit in the topiramate group (P<0.05-0.01), and there were also marked weight loss and W-H ratio reduction at week 8 of follow-up visit in the topiramate group, but the differences in above measurements of three items at other follow-up visit were not found between the two groups. See figure 3 (A-C).

**Adverse Events**

There are 2 cases of outpatients with both dizziness and poor appetite, one case of patient with diarrhea, abnormal liver function and exacerbation of illness in the topiramate group respectively during the trial. Only 2 cases of outpatients with abnormal liver function or 2 cases with exacerbation of illness were reported in the metformin group after 16-week clinical trial respectively. There are no significant differences in above adverse events between the two groups, no other intolerable adverse events, such as
severe organic impairment, were found between the two groups during the trial (P>0.05). One patient presented with worsening psychiatric symptoms in the topiramate group and two patients in the metformin group were found after the end of this study, no significant difference in worsening psychiatric symptoms was found between the two groups.

**Discussion**

Although previous some research suggested that metformin may have robust role of weight loss, this study further indicated that topiramate was significantly superior, at least similar, to metformin in managing established weight gain or obesity caused by some second-generation antipsychotics by ITT and completer analyses in the case of keeping the patient's illness stable and maintaining the original antipsychotic treatment. The benefits from week-4 to 16 of follow-up visit after treatment of concomitant topiramate were emerged whether in terms of weight loss or BMI and waist-hip ratio reduction both by ITT analysis and completion analysis. This also indicated topiramate has a faster and better therapeutic effect on obesity caused by SGAs. Whereas, the effects of concomitant metformin on obesity associated with atypical antipsychotics were not significant, and only waist-hip ratio reduction at week 4 of follow-up visit was remarkably decreased compared with the baseline by ITT analyses and completer analyses. The results associated with topiramate were consistent with most studies' reports and Meta-analyses reviews.\(^5,18,26,27\) Whereas, the results related to metformin in this study were not completely consistent with some previous researches' reports, especially in terms of weight loss.\(^12,13,28\) This may be associated with lower dosage of metformin being used in this study. Topiramate has been approved as a weight loss drug with concomitant use of phentermine by the US Drug Administration (FDA),\(^29\) and most previous studies’ results also revealed that topiramate has a significant antipsychotic effect and weight loss although not all studies’ results related to the effects of topiramate on psychosis are consistent.\(^30,31\)

The comparison between concomitant use of topiramate and metformin revealed that topiramate has a robust therapeutic effect on obesity induced by some SGAs during the vast majority of follow-up visit. This was consistent with most previous Meta-analyses results.\(^5,18\) Nevertheless, it was not consistent with Ellinger's review,\(^9\) which indicated the use of metformin resulted in greater weight loss than topiramte. This perhaps was associated with Ellinger's review without a meta-analyses and statistical test.

It should be noted that, during the trial, the weight at week 8 elevated transitorily in the metformin group, and it did so at week 16 in the topiramate group. All this suggested that outpatients in the real world often can’t follow the experimental requirements, especially in outpatients with mental disorders. They even frantically failed to control their diet and refused to take part in all activities, particularly during episodes of mental illness.

The mechanism of weight loss for topiramate mainly was associated with its decreasing appetite and increasing satiety, but did not change energy expenditure, probably by means of inhibition of carbonic anhydrase.\(^5\) In addition, topiramate itself also played a role in schizophrenia, which was considered to be
mediated by antagonism of glutamate-caused excitotoxicity at the kainic acid (KA) /alpha-amino-3-hydroxy-5-Methylisoxazole-4-propionic acid (AMPA) glutamate receptors.\textsuperscript{32} Altered levels of free glutamate, in which topiramate serves as an antagonist, have been found in schizophrenic patients compared with healthy controls.\textsuperscript{20}

There were no significant differences regarding the rate of lost to follow-up at each follow-up visit, the incidence of adverse events and the number of recurrence of the original mental disorders between the two groups during the trial, this suggested that the tolerance and safety of topiramte and metformin were similar when they were utilized to treat weight gain or obesity induced by SGAs. But this study results were not exactly consistent with some previous reviews or study results.\textsuperscript{5,9} It was perhaps related to the absence of statistical tests about adverse events in these reports.

The use of topiramate, of course, also has some rare adverse events, such as dizziness, diarrhea and inappetence, which should not be ignored although there was no difference between the two groups. However, the diarrhea and inappetence would be significantly alleviated after reducing the dose of topiramate. To be sure, the recurrence or worsening of illness in some outpatients was completely due to non-compliance for the antipsychotic treatment during the trial, it was not associated with the concomitant use of topiramate or metformin although it was not consistent with Choi et al report.\textsuperscript{33}

As to topiramate on maintaining stability in schizophrenia or affective disorders, in this study, only three cases of psychiatric symptoms worsen were found in the topiramate and metformin group after the end of this study, no significant difference was found between the two groups. So, there is not enough evidence that topiramate might stabilize the illness of schizophrenia and affective disorders according to this results.

There are some limitations to this study. Firstly, the dosage of metformin in this study was relatively lower than that in other previous study. This may be one of reasons why metformin reversed antipsychotics-induced obesity was inferior to topiramate. Secondly, the number of cases in the study was relatively small. And the number of completer was also gradually decreased with the increase of follow-up time, which needs to be more concerns in future research although there was no remarkable difference in the rate of loss of follow-up between the two groups.

In summary, in the treatment of weight gain or obesity induced by some SGAs, topiramate holds great promise for reducing weight gain, BMI and waist-hip ratio compared to metformin although metformin may be a more appropriate agent in people with obesity or diabetes. Of course, the ideal approach to weight loss should be also highly individualized, identifying appropriate medications, and behavioral intervention.

**Conclusion**

The topiramate as an adjunctive therapy, similar to metformin in reducing obesity as previously reported, also significantly decrease antipsychotic-induced obesity and waist-hip ratio in patients with
schizophrenia, affective disorder and etc., and has a better acceptability and fewer adverse effects.

**Abbreviations**

BMI: Body mass index; W-H Ratio: Waist-hip ratio; LOCF: Last observation carried forward method; SGAs: Second-generation antipsychotics; H2: histamine 2; ITT: Intention-to-treat.

**Declarations**

**Consent for publication**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ Contributions**

CW and JX designed the study. WS, CH and JZ collected the clinical data and performed the psychiatric assessment. CW analyzed the data and wrote the paper. All authors read and approved the final manuscript.

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Tables

TABLE 1, Comparison of patients’ demographic and clinical features at baseline and after the end of the trial between the two groups
| Variables                        | Topiramate (n) | Metformin (n) | \( \chi^2 / t \) | P value |
|---------------------------------|----------------|---------------|-----------------|---------|
| n                               | 32             | 30            |                 |         |
| Gender (M/F)                    | 28/4           | 24/6          | 0.64            | >0.05   |
| Age (yrs)                       | 32.81±9.11     | 31.87±8.48    | 0.42            | >0.05   |
| Marital status \( M_2 / S_1 / D \) | 9/22/1        | 11/16/3       | 2.09            | >0.05   |
| Occupation (F/J/E)              | 15/13/4        | 16/8/6        | 1.56            | >0.05   |
| Level of education              |                |               |                 |         |
| Primary education               | 15             | 13            | 0.44            | >0.05   |
| Secondary education             | 15             | 16            |                 |         |
| College and above               | 2              | 1             |                 |         |
| Parental obesity                |                |               |                 |         |
| No/Yes                          | 29/3           | 28/2          | 0.15            | >0.05   |
| Diagnosis (S_2/AD)              | 31/1           | 27/3          | 1.21            | >0.05   |
| Inpatients/outpatients          | 2/30           | 0/30          | 1.94            | >0.05   |
| The number of lost to follow-up |                |               |                 |         |
| Lost visit/not lost visit at week 4 | 5/27         | 10/20         | 2.65            | >0.05   |
| Lost visit/not lost visit at week 8 | 6/26         | 11/19         | 2.50            | >0.05   |
| Lost visit/not lost visit at week 12 | 15/17        | 13/17         | 0.08            | >0.05   |
| Lost visit/not lost visit at week 16 | 22/10        | 15/15         | 2.26            | >0.05   |
| CPZ Equivalent daily dose of APS | 433.75±215.57 | 370.17±177.07 | 1.26            | >0.05   |
| Types of APS being used         |                |               |                 |         |
| Clozapine                       | 16             | 10            | 3.15            | >0.05   |
| Olanzapine                      | 6              | 6             |                 |         |
| Quetiapine                      | 2              | 5             |                 |         |
| Resperidone                     | 4              | 6             |                 |         |
| Other APS, and etc.             | 4              | 3             |                 |         |
| Daily dosage of clozapine (n:16,10) | 229.69±121.18 | 165±114.99    | 1.35            | >0.05   |
| Daily dosage of olanzapine (n:6,6) | 10.0±6.32     | 12.08±5.10    | 0.63            | >0.05   |
Table 2 Concomitant APS, affective stabilizers and antidepressants between the two groups

| Variables                                      | Topiramate (n) | Metformin (n) | χ²/t | P value |
|------------------------------------------------|---------------|---------------|------|---------|
| The number of combined use of APS, affective stabilizers and antidepressants | 18            | 27            |      |         |

Types of combined use of APS, and etc.

|            | Topiramate | Metformin | χ²/t | P value |
|------------|------------|-----------|------|---------|
| Clozapine  | 2          | 0         | 11.01| >0.05   |
| Olanzapine | 0          | 3         |      |         |
| Quetiapine | 2          | 1         |      |         |
| Resperidone| 4          | 5         |      |         |
| Zaprosidone| 2          | 1         |      |         |
| Aripiprazole| 2          | 4         |      |         |
| Perphenazine| 4          | 9         |      |         |
| Chlorpromazine| 1          | 0         |      |         |
| Sulpiride  | 0          | 1         |      |         |
| Lithium carbonate| 0    | 1         |      |         |
| Sodium valproate| 0  | 1         |      |         |
| Antidepressants| 1   | 1         |      |         |

CPZ Equivalent daily dose of combined use of APS

|            |            |            |      |        |
|------------|------------|------------|------|--------|
| Topiramate | 242.35±198.26 | 342.50±232.45 | 1.44 | >0.05  |

Note: APS: Antipsychotics, CPZ: Chlorpromazine

Figures
Figure 1

The diagram showing study design and flow of subjects in the study

Figure 2

ITT analyse showed change in weight (A), BMI (B) and W-H ratio(C) during treatment: Compared with baseline : *:P<0.05, **:P<0.001; with metformin:#:P<0.05, ##:P<0.01
Figure 3

Completer analyse showed change in weight (A), BMI (B) and W-H ratio(C) during treatment: Compared with baseline:*:P<0.05, **:P<0.001; with metformin:#:P<0.05,