Effect of Early Intervention with Omega-3 on Insulin Resistance in Patients Initiated on Olanzapine with either Sodium Valproate or Lithium: A randomized, Double-blind, Placebo-Controlled Trial

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Objective: Metabolic side effects of the second generation (atypical) antipsychotics have been a forefront of attention since their availability. One common concern is the development of hyperglycemia and insulin resistance. The aim of this study was to evaluate the effect of early initiation of omega-3 fatty acids supplementation on glucose-insulin homeostasis in a group of psychiatric patients under treatment with olanzapine and sodium valproate or lithium combination.
Method: In a double-blind design, eligible participants with schizophrenia, bipolar I, and schizoaffective disorders who were initiated on olanzapine combination with sodium valproate or lithium were randomly assigned to receive omega-3 or identical placebo capsules for 6 weeks. Fasting blood sugar (FBS), insulin and HbA_{1c} were measured at the baseline and at the end of the 6^{th} week. Homeostatic model assessment of insulin resistance (HOMA-IR), as a measure of insulin resistance, was also determined at the same times.
Results: At the end of the study, no significant difference was observed between the two arms in terms of FBS, fasting insulin, HbA_{1c} and HOMA-IR. However, trends toward decreasing both fasting insulin levels (p= 0.06) and HOMA-IR (p= 0.07) were noted in the group receiving omega-3. No significant changes in the outcome variables were observed from the baseline to the final measurements in both groups.
Conclusion: This study noted that adding omega-3 fatty acids at the commencement of olanzapine combination therapy with valproate or lithium could not favorably influence glucose-insulin homeostasis. However, trends toward a decrease in insulin levels (p= 0.06) and HOMA-IR (p= 0.07) observed in patients receiving omega-3 suggest a possible beneficial role of this supplement in this population and, therefore, warrant further evaluation.

Key words: *Fasting blood sugar, Insulin Resistance, Lithium, Olanzapine, Omega-3, Sodium valproate*

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Insulin resistance, impaired glucose metabolism, hyperglycemia and type 2 diabetes mellitus (T2DM) are the known consequences of treatment with certain antipsychotics and mood stabilizers (1-4). Importantly, patients with schizophrenia, bipolar and schizoaffective disorders have an increased risk of developing obesity, diabetes and metabolic syndrome compared to the general population (3-7). Multiple factors such as genetic and environmental factors as well as the medications inflict higher prevalence of diabetes or abnormal glucose metabolism in this population (4, 8).

Among the second generation antipsychotics, clozapine and olanzapine have a higher inclination to induce diabetes (4, 9) being debated as both weight gain related and weight gain independent (2, 4). Although impairments in insulin secretion have been reported, insulin resistance is the main mechanism involved (4, 10, 11).

Valproate is also associated with obesity related endocrine-metabolic effects (12, 13). Moreover, increase in insulin resistance independent of weight gain has also been reported with valproate (14). Lithium is also linked with excessive weight gain and

obesity (12, 13); however, reports of its effects on glucose-insulin homeostasis are more limited. In particular, it has been implicated that patients receiving polypharmacy are prone to develop more enhanced weight gain (15).

Omga-3 fatty acids in forms of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have shown benefits in prevention of changes in glucose homeostasis and development of T2DM (16). To date, no reports have been made on their beneficial role in psychiatric population receiving medications that cause more metabolic side effects.

Based on the above concerns, the aim of this study was to evaluate the effects of early initiation of dietary doses of omega-3 fatty acids on glucose homeostasis and insulin resistance in a group of psychiatric patients receiving olanzapine combination therapy with either valproate or lithium.

Materials and Methods

We conducted a 6-week double blind, placebo-controlled trial at Roozbeh psychiatric hospital affiliated with Tehran University of Medical Sciences. Participants were diagnosed with schizophrenia, bipolar I disorder or schizoaffective disorder based on DSM-IV-TR criteria. Patients were between 18-60 years of age. Subjects were initiated on olanzapine combined with either sodium valproate or lithium. Any of the 3 mentioned drugs could be initiated simultaneously or within 15 days of the initiation of the first drug .

Patients were excluded if hey had any of the following criteria: (i) previous treatment with the study drugs (olanzapine, sodium valproate, lithium) during the three months prior to the trial participation; (ii) a significant active medical problem or abnormal laboratory tests before trial participation (including: liver function tests ≥ 3 times normal, thyroid stimulating hormone > 4.2 m.I.U/L, GFR< 60 ml/min, fasting blood sugar (FBS) > 125 mg/dl (iii) pregnancy and lactation); (iv) recent (within 4 weeks) consumption of omega-3 fatty acids; (v) BMI ≥ 30 kg/m2; (vi) any contraindication to the study drugs; (vii) patients, or their families refusal for participation; (viii) taking any drug(s) with much known effects on study parameters including drugs used to treat diabetes.

The study was fulfilled in accordance with the Declaration of Helsinki, and was approved by the ethic committee of TUMS. Written informed consent was also obtained .

Participants were randomly assigned to two groups: omega-3 versus placebo. Participants were given omega-3 or identical placebo capsules (double blind) for a total of 6 weeks. An even distribution of participants with positive smoking status and concomitant adjuvant drug received (lithium and valproate) was provided in omega-3 and placebo groups. Each active drug capsule contained 1000 mg omega-3 fatty acids equivalent to 300 mg EPA/DHA. Omega-3 or placebo capsules were titrated up starting with 1 capsule/day in the first intervention week , 2 capsules /day (twice daily) in the second intervention week and 3 capsules/day (in divided doses) from the third intervention week to the end of the study. The omega-3 dosage utilized encompassed the dietary or low dose (< 1 g/day EPA/DHA) supplementation (17).

Each patient was required to remain on his/her olanzapine and mood stabilizer (lithium or valproate) combination protocol throughout the course of the study; however, dosage adjustment was permitted based on the therapeutic level or clinical response (olanzapine could not be increased above 20 mg/day). Since this trial was designed to evaluate a realistic setting, patients were allowed to receive concomitant medications without much affect on the study parameters when confirmed by a clinical pharmacist. The mean of olanzapine, lithium and valproate doses were recorded at the trial initiation, during each week and at the end of the study. Any other medications received by participants during the trial were also recorded.

Blood samples for FBS, insulin, HbA_{1c} were taken at the baseline (before initiation of omega-3 or placebo) and at week 6.

Homeostatic model assessment of insulin resistance (HOMA-IR) was determined as follows: FBS (mg/dl) x fasting insulin (mIU/ml) /405 (18). FBS were measured by enzymatic procedures, fasting insulin by chemiluminescence and HbA_{1c} by the immunoturbidimetry method.

Statistical analysis was carried out with the SPSS statistical package version 15. Demographic characteristics are summarized descriptively and compared using chi-square and independent sample t-test statistical method for qualitative and quantitative data respectively. Baseline characteristics in all variables were recorded prior to the study and were compared using independent sample t-test. Paired t test was carried out as a within group before-after comparison. The end point changes from the baseline were compared for all the variables using independent sample t-test. All the statistical significant tests were 2-sided with a nominal significance level of 0.05.

Results

Forty-one patients completed the 6 week trial (twenty in the omega-3 and twenty one in the placebo group).

No statistically significant differences were observed in the demographic characteristics at the baseline between the two groups (Table 1). The distribution of other medications the participants received during the trial did not differ between the two groups (Table 2). There were no statistically significant differences between the groups in the baseline values of outcome variables.

At the end point, the mean daily dosage of olanzapine was 13.00± 4.97 mg in the omega-3 and 12.85±4.35 mg in the placebo group (p=0.922). In addition, for valproate and lithium, the mean dosage in omega-3 and placebo group were 749.00±189.73 and 608.33±235.32 mg (p=0.170) and 1057.5 ± 288.2 and 1150±300 mg

Table 1. Baseline demographic of patients across treatment groups

	Omega-3	Placebo	P Value
	N=20	N=21	
Age (Year: mean±SD)	31.10±9.98	36.61±10.92	0.100
Gender (n)			
Male	14	17	0.484
Female	6	4	
Diagnosis			
Bipolar I disorder	16	13	0.328
Schizophrenia	3	4	
Schizoaffective disorder	1	4	
Duration of illness (months: mean±SD)	27.20 ± 21.29	34.28 ±32.27	0.414

Table 2. Medications received at any time during the study period

Medication	Number (%) of Participants	
	Omega-3	Placebo
Benzodiazepines		
Clonazepam	14 (70)	14 (66.6)
Lorazepam	2 (10)	1 (4.76)
Chlordiazepoxide	-	1 (4.76)
Typical Antipsychotics		
Haloperidol	12 (60)	13 (61.9)
Chlorpromazine	6 (30)	5 (23.8)
Trifluoperazine	-	1 (4.76)
Flupenthixol Decanoate	1 (5)	1 (4.76)
Atypical Antipsychotics		
Risperidone	2 (10)	2 (9.5)
Other		
Biperiden	12 (60)	13 (61.9)
Promethazine	2 (10)	2 (9.5)
Hydroxyzine	-	1 (4.76)
Propranolol	4 (20)	5 (23.8)
Trazodone	-	1 (4.76)
Ranitidine	1 (5)	-
Omeprazole	-	1 (4.76)

Table 3. Measures at baseline and at the end point

variables	Omega-3		P*	Placebo		P*	Group effect comparison	
	Baseline Mean(SD)	End point Mean(SD)		Baseline Mean(SD)	End point Mean(SD)		t	P**
FBS (mg/dl)	86.00±11.35	84.15±11.19	0.404	86.52±6.61	89.19±10.95	0.275	-1.40	0.169
Insulin (mIU/ml)	13.25±11.94	9.06±7.88	0.065	8.19±6.76	8.00±6.70	0.899	-1.53	0.133
HbA_{1c} (%)	5.14±0.55	5.04±0.77	0.386	5.24±0.59	5.15±0.59	0.608	-.02	0.983
HOMA-IR	3.04±3.19	1.98±1.91	0.070	1.75±1.47	1.75±1.44	0.998	-1.68	0.100

† FBS, fasting blood sugar; HbA_{1c} , hemoglobin A_1c; HOMA-IR, homeostatic model assessment of insulin resistance
* P-values are given for the comparison of before-after changes in each group using paired-samples t-test.
** P-values are given for comparison of end point changes from baseline using independent sample t-test.

(p= 0.502) respectively.

There were no significant changes in FBS, fasting insulin, HbA_{1c} and HOMA-IR within the two groups. Fasting insulin and HOMA-IR decreased after omega-3 administration, but not significantly (Table 3). At the end of week 6, there were no significant differences between the two arms of the study in terms of FBS, fasting insulin, HbA_{1c} and HOMA-IR.

Discussion

According to the results of our study, glucose homeostasis was not favorably influenced by omega-3 fatty acids. It has been shown that in diabetic population fish oil supplementation does not have significant effects on insulin and glucose biomarkers (19, 20).

However, a trend toward a decrease in insulin level and HOMA-IR in our study suggests a beneficial role in decreasing insulin resistance in this population and warrants further evaluation. A decreased level of insulin and HOMA-IR has also been reported after eight week supplementation with EPA plus DHA 2.4 gram/day in chronic renal failure patients on maintenance hemodialysis (21).

It should also be noted that a worsening fasting glucose, HbA_{1c} and insulin profile were not observed in

this study. In our study, HbA_{1c} mean values at baseline in both groups were lower than the 7 percent goal recommended by the American Diabetes Association (ADA) and remained so throughout the study course (22). Correspondingly, studies conducted on the relationship between psychotropic medications and HbA_{1c} levels and the prevalence of abnormal HbA_{1c} levels among psychiatric patients are sparse. One report exhibited 51.9% of the bipolar patients with elevated HbA_{1c} levels (>7%) and mood stabilizer and lithium were associated with a decrease; and further they noted that antipsychotics might be linked with an increase in HbA_{1c} levels in bipolar population (3).

At this time, the medication effects on HbA_{1c} levels, either as monotherapy or in combination regimens, are inconclusive. The unchanged value is related to longer time needed to yield changes in HbA_{1c} levels and may also be related to combined effects of medications on developing diabetes, hyperglycemia and elevated HbA_{1c} .

Increased levels of insulin and HOMA-IR have been observed after 28 days of the treatment with olanzapine (23). Similarly, alteration in blood glucose levels after antipsychotics have been observed only in the first 6 weeks and 8 weeks of the treatment (1, 11). However, our results are consistent with Smith et al who found a fasting glucose within the normal range in olanzapine treated patients (24).Smith et al (25) also evaluated the effects of 5 month monotherapy with olanzapine on fasting glucose, HgA1c and insulin levels and did not observe any changes in FBS, HgA1c, but remarked a significantly greater increase in insulin levels during oral glucose tolerance test (OGTT) compared to the baseline. They concluded that the increase in insulin levels during olanzapine therapy may recompense for the increase in insulin resistance, fasting and postprandial glucose levels. Despite this mechanism proposed, we did not observe a worsening of neither fasting glucose nor insulin levels .

Further studies describing risk factors for development of insulin resistance, elevation of FBS and fasting insulin in medicated psychiatric population are needed to better define patients who benefit most from preventive interventions.

One possible explanation for the unchanged values of FBS in our study is the exclusion of underlying diabetic condition from the study. One study reviewed reports available in WHO database and recognized male gender, an underlying diabetic condition, increase in weight and concomitant use of valproic acid , SSRIs or buspirone as the potential risk factors for developing glucose intolerance for clozapine, olanzapine and risperidone when grouped together (compared with typical antipsychotics) (26).

It should be emphasized that the short duration of this study set limit to observe more profound positive effects. In addition, polypharmacotherapy received by patients during the six weeks of the treatment might have influenced the study results. Additionally, this study did not control diet calories and activity level of the participants. Family history of CVDs and diabetes were not regarded as reliable and thus were not recorded

Conclusion

The addition of dietary (low) doses of omega-3 fatty acids did not produce significant short term improvement in fasting insulin, FBS, HbA_{1c} or insulin resistance at the commencement of olanzapine combined with valproate or lithium in patients with schizophrenia, bipolar I, and schizoaffective disorders. However, a trend towards a decrease in insulin (0.06) and HOMA-IR (p=0.07) necessitates more investigations to define omega-3 fatty acids benefits in this population.

Fasting glucose and insulin profile were not worsened in either group during the 6 week follow-up. Further studies considering risk factors for development of insulin resistance, elevation of FBS and fasting insulin in medicated psychiatric population are needed to better define those patients who benefit most from preventive interventions.

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