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Maternal and neonatal outcomes in pregnant women with gestational diabetes mellitus treated with diet, metformin or insulin

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***Abstract*---**Background; Diabetes mellitus during pregnancy Around 7–10 percent of all pregnancies in the globe are affected with GDM. GDM is more common in pregnant women who are older & more fat. GDM raises the risk of pregnancy problems such as pregnancy-induced hypertension & poor neonatal outcome, as well as development of type two diabetes later in life (T2DM), Aim and objectives; to evaluate maternal & neonatal results in pregnant females with gestational diabetes mellitus handled with diet control, metformin or insulin, Subjects & methods; This was a prospective observational study; 120 patients were being selected from attendee of Obstetrics & Gynecology clinics of AL Hussein University Hospital, All patients were being subdivided into 3 groups, Result; Between 3 categories, there were substantial variances regarding postprandial glycaemia it was substntially lower in category 3 then category 1 with higher level in category 2, Conclusion; Metformin is helpful & safe in treating of GDM, as evidenced by fact that females with GDM who took metformin gained less weight & had better neonatal results than those who took diet or insulin.

***Keywords*---**gestational diabetes, insulin, metformin, neonatal outcomes, pregnant women.

Introduction

Diabetes mellitus during pregnancy about seven-ten percent of total of all pregnancies in the globe are affected with GDM. GDM is more common in pregnant women who are older & more fat. GDM raises the risk of pregnancy problems such as pregnancy-induced hypertension & poor neonatal outcome, as well as development of type two diabetes later in life (T2DM).[1] GDM raises the chances of problems during pregnancy & poor newborn results. Excessive mother-to-fetus glucose transfer raises risk of large or small-for-gestational-year old newborns, neonatal hypoglycemia, & neonatal respiratory distress syndrome, as well as preeclampsia, caesarean section, preterm delivery, & type 2 diabetes mellitus development after pregnancy in females with GDM. Appropriate medication can reduce maternal - fetal morbidity, according to a meta-analysis of multiple randomised trials. For most people, a successful treatment strategy consists of diet alone, with insulin administered if goal blood glucose concentrations are not met with food alone.[2]

Insulin resistance is a characteristic of pregnancy. If there is insufficient insulin production to compensate for insulin resistance, gestational diabetes mellitus (GDM) develops. [3] Women with GDM who were handled with metformin had same, if not good, outcomes than those who were handled just with diet or insulin.[4] Metformin lowers blood sugar levels by reducing hepatic glucose output (gluconeogenesis), improving insulin sensitivity, & increasing peripheral glucose uptake. When compared to diet dependence, weight gain with metformin and insulin treatment is reduced. When glucose management deteriorates due to changes in insulin resistance during pregnancy, these effects may be beneficial.[4] The best diet for women with gestational diabetes is still unknown, & current advice is based on professional opinion. The American Diabetes Association (ADA) recommends dietary counselling (preferably with a trained dietitian) & pregnancy-appropriate diet that limits carbohydrates to thirty five to forty percent of daily calories. Caloric restriction should be used with caution, as 2 studies have found a link between increased maternal serum ketone levels, decreased psychomotor development & IQ in offspring of mothers with gestational diabetes aged 3 to 8 years.[5]

The ADA recommends limiting daily calorie intake by Thirty to thirty three percent (to around 25 kcal per kg of real weight per day) for studied cases with a BMI greater than thirty kg per m2, which avoids ketonemia. Regular exercise has been demonstrated to enhance glycemic control in females with gestational diabetes, but not perinatal results.[6] The study aimed to evaluate Pregnant females with gestational diabetes mellitus who were managed with diet, metformin, or insulin had better maternal & neonatal results.

Materials and Methods

This is an observational research that is being conducted in the future, patients was selected from attendee of Obstetrics & Gynecology clinics of Alhussein University Hospital, Samples were collected by the systematic random method. From June 2021 to June 2022, research protocol is authorised by the Local Ethics Committee, and written informed consents are collected. Sample size: 120

subjects. This study is on a research conducted with Simeonova-Krstevska et al., 2018 Epi Info The sample size was calculated using STATCALC, with the following assumptions: a 95 percent two-sided confidence level & eighty percent power. The odds ratio estimated with a 5percentage error is 1.115. From the Epi- Info output, the final maximum sample size was 113. As a result, the sample size was raised to 120 cases to account for any instances that dropped out during follow-up.

Inclusion criteria: Age: 20- 40 years, gestational diabetes mellitus & Singleton
Exclusion criteria: Pregnant women not known to be diabetic and multiple Pregnancies.

Methods

All patients subdivided into 3 groups: Group (A): Will include metformin was used to cure Forty pregnant females with gestational diabetes mellitus. Group (B): Will include forty pregnant women with gestational diabetes mellitus who were given insulin to treat their condition. Group (C): This group will consist of forty pregnant women who have gestational diabetes mellitus & being treated with a low-carbohydrate diet.

Subjects in each group were:
Consent: following an explanation of the study's details, all test subjects were given both oral & written informed consent, as agreed upon by the ethics committee.
Obstetric past: Gestational year old by last menstrual period dating and Singleton viable fetus.
Medical and operative history: Chronic hypertension, renal disorder, asthma diabetes, herpes simplex infection and previous section or myomectomy.
Physical examination will include: Examination of the whole person includes vital signs such as blood pressure, temperature, & heartbeat, as well as BMI (body mass index). Measured before pregnancy & at delivery, body weight and detection of plasma blood glucose level in each patient twice weekly from the start of diagnosis until delivery.
Abdominal examination: Scar of previous operation
Every group was treated with suggested treatment: Fasting glycaemia of 3.8 to 5.0 Mmol/l & 1 hour postprandial blood glucose concentration of < 7.8 mmol/l were the desired target glucose levels. Based on the glycemic profile, metformin was given at a dose of 500 mg 3 times per day up to a maximum of 2000 mg per day. Diet control in gestational diabetes: Average caloric intake for diabetic patients of average height and normal weight should range between 2200 and 2400 Kcal/day (50-60% CHO, 15-20 % proteins and the remaining fat, divided in 3 main meals and 3 snacks in between). Insulin therapy in gestational diabetes: During 1st trimester, the sum daily insulin demand is 0.7 units/kg/day, while at 2nd trimester, it is 0.8 units/kg/day, at 3rd trimester, it is 0.9–1.0 units/kg/day. Ultrasonography is used to assess foetal growth every four weeks by qualified obstetricians. Neonatal results were defined as a composite of perinatal complications (stillbirth/neonatal death, birth trauma (shoulder dystocia, fracture of the humerus or clavicle, brachial plexus injury), neonatal hypoglycemia, & neonatal hyperbilirubinemia), gestational year old at birth, birth weight, neonate

weighing >4000–4499 g, neonate weighing >4200 g, neonate weighing > 4500 Induction of labour, manner of birth (spontaneous, instrumental (forceps or vacuum extraction), planned caesarean section & secondary caesarean section), gestational hypertension, & preeclampsia, wound healing.

Analyzing data statistically: The IBM SPSS software package version twenty was used to analyse data that was fed into computer. (IBM Corporation, Armonk, NY) Number & % were used to show qualitative information.ShapiroWilk experiment was used to ensure that distribution was normal. Range (minimum & maximum), mean, standard deviation, median, & interquartile range were used to describe quantitative data (IQR). Significance of obtained outcomes was assessed at a 5percentage level.

Results

Table (1): Compare 3 tested categories according to pre- pregnancy BMI, weight gain and gestational week at enrolment

	Category 1 (n = 40.0)	Category 2 (n = 40.0)	Category 3 (n = 40.0)	F	p
Pre- pregnancy BMI (kg/m^2) Min. – Max.	27.00 – 33. 00	27.00 – 33.00	27.00 – 32.00		
Mean ± SD.	29.30 ± 1.92	29.60 ± 1.71	29.30 ± 1.29	0.435	0.648
Median (IQR)	29.0(28.0 – 30.0)	29.0(29.0 – 30.0)	29.0(29.0 – 30.0)		
Weight gain (kg) Min. – Max.	07.00 – 12.00	8.00 – 13.00	10.00 – 15.00		
Mean ± SD.	9.10 ± 01.60	9.90 ± 1.60	11.40 ± 1.71	20.398*	<0.001*
Median (IQR)	9.0(8.0 – 10.0)	9.50(9.0 – 11.0)	10.50(10.0 – 13.0)		
Sig. bet. grps.	p_1=00.077,p_2<00.001*,p_3<00.001*				
Gestational week at enrolment (g.w.) Min. – Max.	27.00 – 34.00	25.00 – 32.00	27.00 – 32.00		
Mean ± SD.	29.50 ± 2.04	28.90 ± 2.05	29.30 ± 1.57	1.035	0.358
Median (IQR)	29.0(28.0 – 30.0)	29.0(28.0 – 30.0)	29.0(28.0 – 30.0)		

IQR: Inter quartile range SD: Standard deviation

F: F for One way ANOVA examine, Pairwise compare 2 categories was done by Post Hoc

Test (Tukey) p: p ratio to compare tested categories p_1: p ratio to compare category 1 & category 2 p_2: p value to compare category 1 & category 3 p_3: p value to compare category 2 & category 3

*: Scientifically important at p ≤00.05

There were insignificant differences between three groups as regard Pre-pregnancy BMI (kg/m^2), and Gestational week at enrolment (g.w.) but as regard

weigh gain it was significantly higher in group C versus other two groups. Table (1)

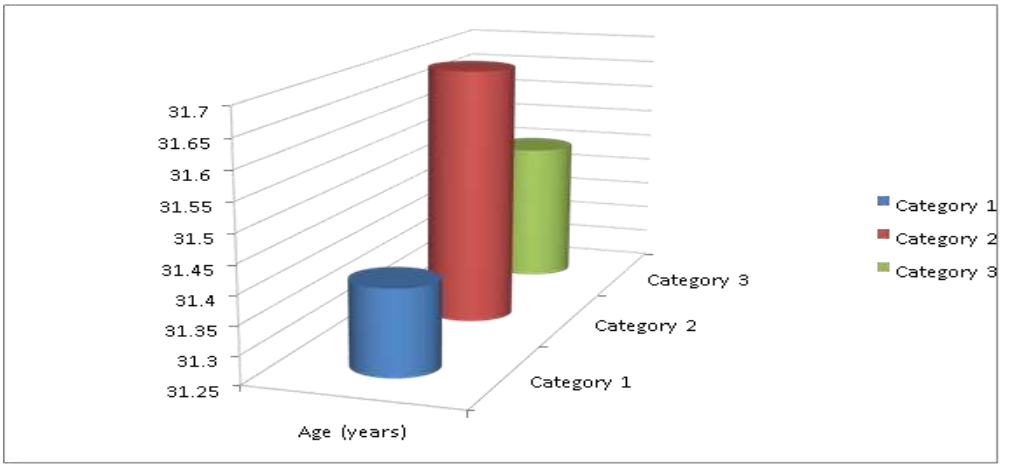

Figure1. Compare 3 tsted categories according to years old

There were insignificant differences between three groups as regard age

Table (2): Compare 3 tested categories according to HbA1c

HbA1c at 37 g.w.	Category 1 (n = 40.0)	Category 2 (n = 40.0)	Category 3 (n = 40.0)	F	p value
Min. – Max.	4.80 – 6.0	5.90 – 7.10	4.80 – 6.0		
Mean ± SD.	5.35 ± 0.37	6.48 ± 0.40	5.34 ± 0.33	128.665*	<0.001*
Median (IQR)	5.30(5.1 – 5.7)	6.45(6.2 – 6.8)	5.40(5.1 – 5.4)		
Sig. bet. grps.	p_1<00.001*,p_2=00.992,p_3<00.001*				

IQR: Inter quartile range SD: Standard deviation
F: F for One way ANOVA examine , Pairwise compare two categories was done by Post Hoc examine (Tukey) p: p ratio to compare tested categories p_1: p to compare category 1 & category 2 p_2: p to compare category 1 * category 3 p_3: p to compare category 2 & category 3
*: Scientifically important at p ≤ 00.05

As regard HbA1c at 37g.w it was importantly lower in category 1 & 3 than in category 2 it was importantly higher. Table (2)

Table (3): Compare between 3 tested categories according to fasting glycaemia

Fasting glycaemia (mmol/l)	Category 1 (n = 40.0)	Category 2 (n = 40.0)	Category 3 (n = 40.0)	F	p
Min. – Max.	5.0 – 6.20	5.60 – 7.0	5.0 – 6.0		
Mean ± SD.	5.58 ± 0.33	6.08 ± 0.49	5.37 ± 0.32	35.593*	<0.001*
Median (IQR)	5.60(5.4 – 5.7)	5.80(5.8 – 6.2)	5.35(5.1 – 5.6)		
Sig. bet. grps.	p_1<00.001*,p_2=0.044*,p_3<00.001*				

IQR: Inter quartile range SD: Standard deviation

F: F for One way ANOVA examine, Pairwise compare two categories was done by Post Hoc
Examine (Tukey) p: p ratio to compare tested categories p_1: p ratio to compare category 1& category 2 p_2: p ratio to compare category 1 & category 3 p_3: p ratio to compare category 2 & category 3
*: Scientifically important at $p \leq 0.05$

There were important variations in 3 categories as Fasting glycaemia (mmol/l) it was raised in category 2 than group 1 & 3. Table (3)

Table (4): Compare 3 tested categories according to neonatal result

Neonatal outcome	Category 1 (n = 40.0)		Category 2 (n = 40.0)		Category 3 (n = 40.0)			Examine of Sig.	p
	No.	%	No.	%	No.	%			
Perinatal complications No Birth trauma	40 0	100.0 0.0	40 0	100.0 0.0	36 4	90.0 10.0		x^2= 5.912*	MCp= 0.036*
Gestational age at delivery (g.w.) Min. – Max. Mean ± SD.	37.0 – 39.60 38.45 ± 0.90		36.0 – 39.60 37.60 ± 1.36		37.0 – 39.60 38.35 ± 0.89			F= 7.536*	0.001*
Median (IQR)	38.70(38.0 – 39.0)		37.50(36.0 – 38.9)		38.25(38.0 – 39		.0)		
Sig. bet. grps.	p_1=00.002*,p_2=0.908,p_3=00.006*								
Birth weight (gr) Min. – Max. Mean ± SD.	2.80 – 4.30 3.49 ± 0.41		3.0 – 4.50 3.62 ± 0.39		3.30 – 5.0 3.77 ± 0.50			F= 4.346*	0.015*
Median (IQR)	3.52(3.2 – 3.7)		3.6.0(3.40 – 3.80)		3.6(3.4.0 – 3.9.		0)		
Sig. bet. grps.	p_1=00.344,p_2=00.011*,p_3=00.273								
Prematurity	4	10.0	0	0.0	0	0.0		x^2=5.912	MCp=0.036*
LGA	0	0.0	8	20.0	16	40.0		x^2=20.0*	<0.001*
SGA	4	100.0	0	0.0	0	0.0		x^2=5.912	MCp=0.036*
% with hypoglycaemia	8	20.0	20	50.0	16	40.0		x^2=8.038*	0.018*
Neonatal hyperbilirubinaemia	4	10.0	8	20.0	4	10.0		x^2=2.308	0.315
Apgar score at 5 Min. – Max. Mean ± SD.	6.0 – 9.0 7.90 ± 0.84		6.0 – 9.0 7.50 ± 0.93		6.0 – 9.0 7.30 ± 0.91			F= 4.647*	0.011*
Median (IQR)	8.00(8.0 0 – 8.00)		8.00(7.0 – 8.00)		7.00(7.00 – 8.00)				
Sig. bet. grps.	p_1=0.118,p_2=0.009*,p_3=0.580								
Need for respiratory	0	0.0	4	10.0	8	20.0		x^2=9.488*	MCp=0.00

support									6*
Admission to the neonatology department	8	20.0	16	40.0	16	40.0		x^2=4.800	0.091

IQR: Inter quartile range SD: Standard deviation
χ^2: Chi square examine MC: Monte Carlo
F: F for One way ANOVA examine, Pairwise compare two categories was done by Post Hoc
Examine (Tukey) p: p ratue to compare tested categories p_1: p ratue to compare category 1 & category 2 p_2:p ratue to compare category 1& category 3 p_3: p ratue to compare category 2 & category 3
*: Scientifically important at p ≤ 00.05

As regard neonatal outcome there was perinatal complications in group C only, Gestational year old at delivery (g.w.) was importantly lower in category 2 than other groups, as regard birth weight it was rised in group C than other groups with significant differencesPrematurity , SGA founded only in group A cases , LGA significantly founded in group C , % with hypoglycae-mia and Neonatal hyperbilirubinaemia significantly founded in group B , Regarding apgar score it was higher in group A than other groups , Need for respiratory Support was importantly founded in category 3 than other categories , Admission to the neonatology department was significant differences between three groups. Table (4)

Table (5): Compare 3 tested categories according to maternal outcome

Maternal outcome	Category 1 (n = 40.0)		Category 2 (n = 40.0)		Category 3 (n = 40.0)		χ^2	p
	No.	%	No.	%	No.	%		
Preeclampsia	4	10.0	8	20.0	4	10.0	2.308	0.315
Gestational hypertension	4	10.0	12	30.0	8	20.0	5.00	0.082
Mode of delivery Assisted	4	10.0	4	10.0	0	0.0		
Spontaneous	8	20.0	4	10.0	0	0.0	15.329*	^{MC}p= 0.002*
Caesarean section	28	70.0	32	80.0	40	100.0		

χ^2: Chi square test MC: Monte Carlo
p: p ratio to compare tested categories
*: Scientifically important at p ≤ 00.05

As regard maternal outcome there was important differences between 3 categories regarding preeclampsia occurrence or gestational hypertension but as regard mode of delivery there was significant differences. Table (5)

Discussion

This was a prospective observational study; 120 patients were being selected from attendee of Obstetrics & Gynecology clinics of AL Hussein University Hospital, studied cases were being subdivided into 3 categories: Group (A): included 40

pregnant females with gestational diabetes mellitus treated with Metformin. category (B): included 40 pregnant females with gestational diabetes mellitus dealed with insulin. Group (C): included 40 pregnant females with gestational diabetes mellitus dealed with diet control.

Analysis of our findings revealed that the mean ± SD of age in category 1 was 31.40 ± 2.76, in category 2 was 31.70 ± 2.76 and in category 3; the age was 31.50 ± 2.18. There were insignificant differences between three groups as regard age.
In comparison with our results, Simeonova-Krstevska et al. 4 found that 200 GDM pregnancies were handled with diet alone, 101 with insulin, & 48 with metformin in a study of 349 GDM pregnancies. Diet-treated women have a lower BMI before pregnancy but a higher weight increase throughout pregnancy than the other 2 categories, as can be observed. The metformin group gained the least weight. Insulin-treated participants enrolled in the research earlier than those in other groups. There were no distinct changes in incidence of smoking cigarettes or a family history of diabetes across the 3 categories.

Furthermore, a total of 124 females were in research of Abbas et al., 2021 which reported that the mean ± SD of age in category 1 (insulin) was 31.40 ± 2.76, in category 2 (metformin) was 31.70 ± 2.76. Also, the mean year old scores of insulin & metformin groups were comparable (30.76.4 years & 28.85.7 years, respectively, P value=00.49), according to Najafian et al., 7. The average age of all women was 18 years old, with the lowest & highest ages being 18 & 47 years old, respectively. In current study, we found that there were insignificant differences between three groups as regard Pre- pregnancy BMI (kg/m2), and Gestational week at enrolment but as regard weigh gain it was significantly higher in group C versus other two groups.

Diet-treated women have a lower BMI before pregnancy but a higher weight gain while pregnancy than other 2 categories, according to Simeonova-Krstevska et al., 4. The metformin group gained the least weight. Insulin-treated participants enrolled in the research earlier than those in other groups. In agreement with findings, Abbas et al., 2021 which reported there were insignificant differences between three groups as regard Pre- pregnancy BMI (kg/m2), and Gestational week at enrolment but as regard weigh gain Average rate of maternal weight gain per week was 562.7 ± 111.7 gm/week in the insulin group and 453.2 ± 99.58 gm/week in the metformin group.

Outcomes of our research reported the rate of maternal weight gain per week was statistically importantly lower in metformin category compared to the insulin category. In their study, Priya and Kalra, [8] agreed with our findings regarding weight gain during pregnancy in those on metformin as first line therapy compared with those on insulin. Many studies showed the same significant difference in weight gain such as Ainuddin et al., [9] as well as Iftakhar, [10]. However, it is worth mentioning that our study is unique in comparing weight gain rate per week, not only comparing the starting and the end of pregnancy weight, which might be affected by duration of follow up or timing pregnancy.

In meta- analysis of Moosazadeh et al., [11] they have 2697 females with a family past of diabetes mellitus, 29134 females without in the meta-analysis method,

which included 33 relevant papers with 2516 articles. 954 & 4372 individuals, respectively, developed GDM. Using the metaanalysis method to combine the data of the primary investigations, the total odds value of having a family history for development GDM was estimated to be 3.46. (95 percent CI: 2.80-4.27). Moreover, Simeonova-Krstevska et al., [4] 200 GDM pregnancies were managed with diet alone, 101 with insulin, & 48 with metformin, according to the study. There were no distinct changes in incidence of smoking cigarettes or a family history of diabetes across the 3 categories.

At meta-analysis of Yu et al., 12 Twenty of 23 studies studied quantitatively reported both baseline & end glucose levels. For ITT studies, the differences from baseline were computed using reported baseline & post-treatment blood glucose concentrations. Ben-Haroush et al. 13 found that the metformin group had importantly lower baseline FBG than the insulin category (104 13.12 mg/dl vs. 117.9 29.06 mg/dl). Mukhopadhyay et al., 14 reported that glyburide category had significantly lower baseline 2HPG levels (184.1 20.46 mg/dl vs. 194.3 18.47 mg/dl) than the insulin category. Both trials were included in meta-analysis since variations in FBG, 2HPG, & HbA1c from baseline were calculated.

Fasting glucose levels were statistically considerably lower in metformin category compared to the insulin category, according to Abbas et al., 15, albeit with limited clinical relevance. There were no scientifically important variations between 2 groups in postprandial glucose levels or glycosylated haemoglobin. In contrast to our study, Bansal et al., [16] the insulin group had slightly higher postprandial glucose readings after 2-hours of oral glucose than the metformin group, according to the study. Also, Waheed et al., [17] found that in pregnant studied cases, there was no discernible variations in efficacy of metformin or insulin in managing diabetes. However, these disagreements may be due different insulin regimen.

Balsells et al., [18] compared effects of metformin vs. insulin on foetal & maternal results in a meta-analysis. They discovered that the maternal weight growth & neonatal hypoglycemia varied widely between metformin & insulin. Metformin has been shown to be slightly more effective than insulin. Hypoglycemia is a common occurrence in babies of GDM mothers. Abbas et al., [15] there were no wide variations in the incidence of foetal macrosomia between the 2 groups of women (22.2 percent in insulin category & 13.7 percent in metformin category, respectively) P = 0.31). In agreement with us, Rachel et al., 2017 study found that there was no variation between two categories regarding incidence of macrosomia.

Also, Mesdaghinia et al., [18] found that no statistical difference regarding incidence of macrosomia between insulin & metformin groups. In contrast, Priya and Kalra, [8] study in found that women on metformin had lower risk of fetal macrosomia compared to insulin group. These disagreements may be due to the difference in the gestational ages at enrolment, therapeutic regimens used and compliance of pregnant women included in the studies. Finally, as regard maternal outcome; we found that there was important differences between three categories regarding preeclampsia occurrence or gestational hypertension but as regard mode of delivery there was significant differences.

Moreover, Abbas et al., 2021 study found no statically significant difference between insulin and metformin groups regarding pregnancy induced hypertension (1.8% vs 7.8% in insulin and metformin groups respectively). In contrast to our study, Zhao et al., 2015 Metformin showed a substantial effect on pregnancy-induced hypertension, according to the study [RR 0.54; 95 percent confidence interval (CI) 0.31; 0.91]. Also, Hayer et al., 2009 found that incidence of preeclampsia is rise in insulin category to in metformin category (P value = 00.06). These disagreements may be due different inclusion and exclusion criteria as we exclude many risk factors of having medical disorders as gestational hypertension. In conclusion, metformin is useful & safe in the cure of GDM, according to current understanding, because females with GDM who took metformin gained less weight & had better neonatal results than those who took diet or insulin. However, it is unknown if prenatal exposure to an insulin-sensitizing drug like metformin is useful or detrimental, thus it should be used with caution during pregnancy.

Conclusion

Metformin is helpful & safe in cure of GDM, as evidenced by fact that females with GDM who took metformin gained less weight & had better neonatal outcomes than those who took diet or insulin.

Conflict of interest: There are no conflicts of interests.

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