THE IMPACT OF hsCRP LEVELS ACROSS GLUCOSE TOLERANCE CATEGORIES: FROM NORMAL GLUCOSE TOLERANCE TO ESTABLISHED DIABETES

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ABSTRACT

Objective: *To determine if there is an impact of high sensitive C-reactive protein (hsCRP) levels across different glucose tolerance categories.*

Material and Method: *Data derived from recently completed population-based survey, 'The Prevalence of Diabetes, Obesity, Hypertension and Endocrine Disease in Turkey' (TURDEP-II), which was performed in adult population (20+ years, n=26,499, 63% women).*

Results: *In women mean (±SEM) concentration of hsCRP was significantly higher than in men (3.95±0.05 vs. 3.53±0.09 mg/L, p<0.001). In general hsCRP (controlled for age, gender, and living environment) correlated positively with BMI, waist, fasting plasma glucose (FPG), 1-hPG, 2-hPG, insulin, HbA1c, HOMA-IR, eGFR, but inversely with HDL-c.*

Univariate variance analysis (adjusted for age, gender, living environment, BMI, waist, BP, and lipids) revealed that hsCRP significantly differs across glucose tolerance status (p<0.001). Ad-hoc comparisons indicated that hsCRP (mg/L) in normal glucose tolerance (NGT: 3.49±0.13) group is significantly lower than isolated impaired fasting glucose (i-IFG: 4.13±0.25, p=0.023), combined glucose intolerance (CGI=IFG + impaired glucose tolerance [IGT]: 4.49±0.33, p=0.006), new diabetes mellitus (new-DM: 5.65±0.35, p<0.001) and known-DM (4.61±0.33, p=0.002) groups. However, hsCRP in new-DM group was significantly higher than all other categories (NGT: p<0.001, i-IFG: p<0.001, i-IGT: p=0.001, CGI: p=0.014, and known-DM: p=0.026).

Conclusion: *According to the results from this large population-based survey, hsCRP levels showed a progressively increasing trend from NGT through new-DM categories. Any abnormality of glucose tolerance (either pre-DM or DM) is associated with subclinical inflammation. However, when the disease established, the influence of inflammatory process might become lesser than the earlier metabolic derangements.*

Keywords: *New diabetes, known diabetes, impaired fasting glucose, impaired glucose tolerance, hsCRP levels.* ***Nobel Med 2016; 12(2): 38-44***

NORMAL GLUKOZ TOLERANSINDAN YERLEŞMİŞ DİYABETE, GLUKOZ TOLERANS KATEGORİLERİNDE hsCRP DÜZEYLERİNİN ETKİSİ

Amaç: Bu çalışmada yüksek duyarlıklı C-reaktif protein (hsCRP) düzeylerinin farklı glukoz tolerans gruplarındaki etkilerinin belirlenmesi amaçlandı.

Materyal ve Metot: Araştırmada yetişkin toplumda yeni tamamlanan 'Türkiye Diyabet, Hipertansiyon, Obezite ve Endokrin Hastalıklar Prevalans Çalışması'nın ('TURDEP-II', yaş: 20+, n=26.499, %63 kadın) verileri kullanıldı.

Bulgular: Kadınların ortalama(±SEM) hsCRP düzeyleri, erkeklerden anlamlı olarak daha yüksekti (3,95±0.05 vs. 3,53±0.09 mg/L, p<0,001). Yaş, cinsiyet ve yaşanılan çevreye göre kontrol edilmiş hsCRP düzeyleri: BKİ, bel çevresi, açlık plazma glukoz (APG), 1-stPG, 2-stPG, insülin, HbA1c, HOMA-IR ve eGFR ile pozitif; HDL-k ile negatif korelasyon gösterdi.

Tek yönlü varyans analizi ile (yaş, cins, yaşanılan çevre, BKİ, bel çevresi, kan basıncı ve lipid düzeylerine göre ayarlama yapıldıktan sonra) hsCRP düzeyleri, glukoz tolerans gruplarında anlamlı ölçüde farklıydı (p<0,001). Grupların karşılaştırmalarında; hsCRP düzeylerinin (ortalama±SEM; mg/L) normal glukoz toleranslı grupta (NGT: 3,49±0,13) izole bozulmuş açlık glukozu (i-BAG: 4,13±0.25, p=0,023), kombine glukoz intoleransı (KGİ=BAG + bozulmuş glukoz toleransı [BGT]: 4,49±0,33, p=0,006), yeni diabetes mellitus (yeni-DM: 5,65±0,35, p<0,001) ve bilinen-DM (4,61±0,33, p=0,002) gruplarının herbirinden daha düşüktü. Diğer taraftan, yeni DM grubunda hsCRP düzeyleri diğer tüm glukoz toleransı kategorilerinden (NGT: p<0,001, i-BAG: p<0,001, i-BGT: p=0,001, KGİ: p=0,014 ve bilinen-DM: p=0,026) daha yüksek bulundu.

Sonuç: Toplum-temelli ve yüksek sayıda bireyi içeren bu çalışmanın sonuçlarına göre, hsCRP düzeyleri NGT'den yeni-DM kategorilerine doğru giderek artmaktadır. Glukoz toleransındaki (pre-DM ve DM) herhangi bir bozukluğun subklinik inflamatuvar süreç ile ilişkili olduğu görülmektedir. Bununla beraber, yerleşmiş DM'de inflamatuvar sürecin etkisi metabolik bozukluğun daha erken dönemlerine göre azalmış olabilir.

Anahtar kelimeler: Yeni diyabet, bilinen diyabet, bozulmuş açlık glukozu, bozulmuş glukoz toleransı, hsCRP düzeyleri. **Nobel Med 2016; 12(2): 38-44**

INTRODUCTION

Diabetes mellitus (DM) is one of the strong major risk factors of cardiovascular disease, and its prevalence is increasing worldwide.[1] The relation between chronic subclinical (low-grade) inflammation and insulin resistance (IR) has been previously described.[2,3] In fact, peripheral IR is known as a high risk factor for type 2 diabetes (T2DM) and it is also associated with concomitant morbidities such as hypertension (HT), hyperlipidemia (HL) and cardiovascular disease (CVD).[2,3]

C-reactive protein (CRP) is an acute phase protein, synthesized predominantly by the liver and has been used as a marker of systemic inflammation.[4-6] Both prospective and cross-sectional studies have shown that high-sensitive CRP (hsCRP) is associated with increased risk of diabetes, prediabetes, cardiovascular disease, metabolic syndrome (MS), obesity and IR.[2-4,7-12] Moreover, it has been reported that elevation in hsCRP is an indicator of future development of T2DM.[11,12] These findings suggest that inflammation closely associated with pathogenesis of glucose metabolism. However, the mechanism of behind this is not completely understood, and it is not clear whether the relationship between the levels of hsCRP and progress of glucose tolerance from normal to diabetes is an ongoing process.

The purpose of the present study is to determine whether hsCRP levels differ between glucose tolerance categories, and to evaluate if there is a continuous relationship between low-grade inflammation and the progress of the metabolic status.

MATERIAL AND METHOD

Data derived from recently completed population-based survey 'The Turkish Epidemiology Survey of Diabetes, Hypertension, Obesity and Endocrine Diseases (TURDEP-II).[13] We included people from 270 urban and 270 rural centers in Turkey, who were randomly selected and invited, and according to the age distribution of Turkish adult population. TURDEP-II field survey was performed with an 85% participation rate. The protocol was described in our previous report.[13] The study included 26,499 subjects aged 20 years and over (63% women).

Detailed medical histories of each participant were questioned, and anthropometric (height, weight, waist

and hip circumference) and blood pressure (BP) measurements were done. Body Mass Index (BMI), waist-to-hip ratio (WHR) were calculated accordingly.[14]

Blood glucose concentration was measured using a glucometer, which uses a glucose oxidase method of estimation and gives results calibrated for plasma glucose (PG). All other biochemical tests including glucose, insulin, lipid profile, were measured via Roche Diagnostics Modular Auto analyzer System in Central Biochemistry Laboratory of Istanbul University Istanbul Faculty of Medicine. Levels of hsCRP were analyzed by immunoturbidimetric assay (Roche/Hitachi 912, MODULAR P analyzers: ACN 210. CRPL3 titan-quant, CRP gen.3), and hemoglobin A1c (HbA1c) by turbidimetric inhibition immunoassay; both the system and the laboratory have been regularly certified (Roche Diagnostics TQ HbA1c Gen. 3 NGSP Certificate).

All patients measured fasting plasma glucose (FPG) and HbA1c, had a oral glucose tolerance test (OGTT) with 1-hPG and 2-hPG. A FPG between 100-125 mg/dL but 2-hPG<140 mg/dL was considered 'isolated IFG' (i-IFG); persons with 2-hPG 140-199 mg/dL but FPG<100 mg/dL were considered 'isolated IGT' (i-IGT), and persons with FPG between 100-125 mg/dL and 2-hPG 140-199 mg/dL was accepted as 'combined glucose intolerance' (CGI: IFG+IGT). A FPG≥126 mg/L and/or a 2-hPG≥200 mg/L were considered new-DM.[15-17] HOMA-IR (homeostasis model of assessment=FPG (mg/dL) x fasting insulin (μU/mL)/405), and nonHDL-cholesterol (nonHDL-c=total cholesterol-HDL-c) were calculated accordingly. Glomerular filtration rate (eGFR) was estimated using Cockroft equation.[18] Patients with known systemic or infectious diseases were excluded from the analysis.

The study protocol was approved by the Istanbul Faculty of Medicine Ethical Committee (2008/699). A written informed consent was obtained from each participant and the study was conducted in accordance with the Declaration of Helsinki.

Statistics

All analyses were performed using SPSS for Windows (version 19.0; SPSS IBM, Chicago, IL). Descriptive statistics were performed using t test for comparisons between genders. Partial correlation of hsCRP controlled for age, gender, rural/urban, region, BMI, waist was determined to evaluate if there is any association of FPG and 1-hPG, 2-hPG, and HDL-c, insulin, HbA1c, HOMA-IR and eGFR with hsCRP. Univariate analysis was used to assess if there is any difference of hsCRP levels across the glucose tolerance categories, hsCRP levels were adjusted for age, gender, urban/rural, region, BMI, waist, sBP, dBP, HDL-c, and nonHDL-c. *p* values less than 0.05 considered statistically significant.

RESULTS

Characteristics of the men and women participants are shown in Table 1. Men were significantly older; and had higher mean weight, WHR, waist, sBP, dBP, creatinine, triglycerides (TG) and nonHDL-c values than women. However, women had significantly higher mean BMI, hip, pulse, FPG, HbA1c, 1-hPG, 2-hPG, and HDL-c. Fasting insulin, eGFR and HOMA-IR values did not differ significantly between genders. In women, the mean (±SEM) concentration of hsCRP was significantly higher than in men (3.95±0.05 vs. 3.53±0.09 mg/L, $p<0.001$).

In the study population the prevalence of i-IFG was 14.7% and i-IGT 7.9%, CGI 8.2%, new-DM 7.5%, and known-DM 8.0%. The mean (±SD) duration of diabetes in the previously known-DM group was 6.6±5.7 years.

The mean levels of hsCRP controlled for age, gender, urban/rural, and region positively correlated with BMI, waist, FPG, 1-hPG, 2-hPG, insulin, HbA1c, HOMA-IR and eGFR; whereas hsCRP was inversely correlated with HDL-c only (Table 2).

Univariate analysis corrected for age, gender, urban/rural, region, BMI, waist, BP, lipids, and hormones revealed that hsCRP significantly differ across glucose tolerance status ($p<0.001$). Ad hoc comparisons indicated that hsCRP (mean±SEM) in the normal glucose tolerance group (NGT: 3.49±0.13 mg/L) is significantly lower than i-IFG, CGI, new-DM and known-DM groups (i-IFG: 4.13±0.25 mg/L, $p=0.023$; CGI: 4.49±0.33 mg/L, $p=0.006$; new DM: 5.65±0.35 mg/L, $p<0.001$; known DM: 4.61±0.33 mg/L, $p=0.002$). On the other hand, hsCRP in the new-DM group was significantly higher than all other glucose tolerance categories (NGT: $p<0.001$, i-IFG: $p<0.001$, i-IGT: $p=0.001$, CGI: $p=0.014$, and known-DM: $p=0.026$ [Figure and Table 3]).

DISCUSSION

Subclinical inflammation has been linked with the development of T2DM. Evidence predominantly come from previous studies demonstrating associations between mildly elevated levels of circulating acute phase markers such as CRP, and indices of IR and diabetes.[4-6] However, the mechanisms are not fully understood; genetic and environmental factors such as infections and over nutrition are believed to contribute it is not clear whether inflammation is the cause or the consequence of these disorders.[2-6]

Inflammation may have linked to increased body weight and induce IR and hyperglycemia or it may have a direct effect on IR, or hyperglycemia per se may trigger inflammation and thus, DM may develop.[2,3,10-12,19,20] It has been suggested that obesity, particularly central obesity directly responsible from elevated CRP and inflammatory cytokines, and low-grade inflammation is a consequence rather than a cause of IR.[21,22] Nevertheless, there are controversies between studies. Rhee et al evaluated that the mean hsCRP levels increased significantly as the FPG level increased and this association was lost after adjustment for age and BMI in healthy Koreans.[23] Another studalso demonstrated a strong association of fasting insulin with CRP concentration even after adjusting for BMI.[4] Marques-Vidal *et al*. showed that subjects with diabetes and IGT had higher hsCRP levels than subject with NGT and IFG, this difference was lost after adjusting for age, gender and BMI.[24] In our study we found after adjusted with age, gender, urban/rural, and region correlation between hsCRP positively correlated with BMI, waist circumference, FPG, 1-hPG and 2-hPG, HbA1c, fasting insulin, HOMA-IR and eGFR; whereas hsCRP was negatively correlated with HDL-c.

Furthermore, there is debate as to whether this inflammation is an ongoing process starting from mild abnormality of glucose metabolism and continues to increase to develop diabetes. This can be resolved by well-designed, large studies evaluating the population from normal glucose metabolism to full-blown diabetes. Nevertheless, the number of studies evaluated the role of hsCRP across all categories of glucose metabolism (i.e. from normal glucose tolerance to established diabetes) in the same population is very limited.

In this study hsCRP showed a strongly increasing trend from NGT to new-DM. The trend did not change when hsCRP adjusted for age, gender, living environment and region; and it was continued even after further adjustments for BMI, waist, BP, lipids, and serum creatinine levels were done. The mean concentration of hsCRP in the NGT group was lower significantly than in all other glucose tolerance categories except that i-IGT, which showed numerically but not significantly higher level. Whereas the mean concentration of hsCRP was highest in the new-DM group.

A recent meta-analysis included ten prospective studies showed that elevated IL-6 and CRP levels were significantly associated with future development of T2DM.[12] Festa *et al.*, reported post OGTT glucose rather than FPG levels were strongly correlated to baseline CRP levels.[25]

Recently it has been shown that glucose-hsCRP relationship is stronger for 2hPG levels than for FPG levels.[25-28] In Mexican elevated hsCRP levels was

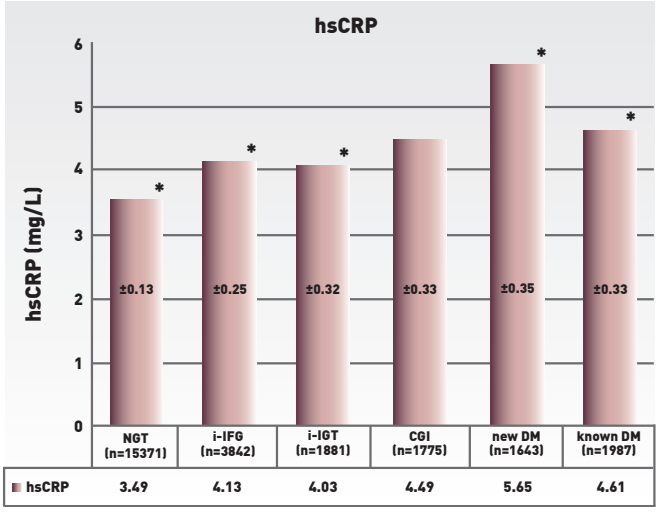

Figure. Mean (±SEM) concentrations of hsCRP across glucose tolerance status**
hsCRP: High sensitive C-reactive protein, **CGI:** combined glucose intolerance (IFG+IGT), **i-IFG:** isolated impaired fasting glucose, **i-IGT:** isolated impaired glucose tolerance, **known DM:** previously diagnosed diabetes mellitus, **NGT:** normal glucose tolerance, **new DM:** newly diagnosed diabetes mellitus, **SEM:** ±standard error of mean, **BMI:** body mass index, **sBP and dBP:** systolic and diastolic blood pressure, **HDL-c:** high density lipoprotein cholesterol, *: for p values, **: hsCRP adjusted for age, gender, urban/rural, region, BMI, waist, sBP, dBP, HDL-c, non-HDL-c, and creatinine

Table 1. General features of the TURDEP-II population

	Women (n=16242) mean±SD (95% CI)	Men (n=9061) mean±SD (95% CI)	*p*
Age (year)	44.7 ± 15.1	46.3 ± 15.8	<0.001
Height (cm)	158.6 ± 6.8	171.2 ± 7.3	<0.001
Weight (kg)	73.1 ± 14.6	80.3 ± 13.6	<0.001
BMI (kg/m2)	29.1 ± 5.9	27.2 ± 4.4	<0.001
Waist (cm)	92.8 ± 14.8	97.1 ± 13.0	<0.001
Hip (cm)	109.6 ± 13.5	105.5 ±10.6	<0.001
WHR	0.846 ± 0.087	0.921 ± 0.087	<0.001
sBP (mmHg)	119.9 ± 26.59	121.1 ± 22.54	<0.001
dBP (mmHg)	74.5 ± 13.4	75.3 ± 12.6	<0.001
Pulse (beat/min)	79.7 ± 9.0	78.5 ± 9.2	<0.001
FPG (mg/dL)	97.5 ± 35.4	98.1±37.7	<0.001
1-hPG (mg/dL)	162.9 ± 46.4	159.4 ± 46.1	<0.001
2-hPG (mg/dL)	131.5 ± 39.9	115.9 ± 38.4	<0.001
HbA1c (%)	5.8 ± 1.1	5.75 ± 1.2	0.005
Fasting insulin (µU/mL)	8.5 ± .7	8.4 ± 13.1	0.591
HOMA-IR	2.17 ± 2.92	2.16 ± 3.72	0.298
TG (mg/dL)	125.8 ± 78.5	150.4 ± 106.6	<0.001
HDL-c (mg/dL)	50.0 ± 12.5	41.8 ± 10.3	<0.001
NonHDL-c (mg/dL)	137.1 ± 40.1	143.2 ±39.6	<0.001
Creatinine (mg/dL)	0.73 ± 0.13	0.93 ± 0.17	<0.001
eGFR (mL/min per 1.73 m2)*	118.8 ± 33.1	115.2 ± 32.2	0.068
hsCRP (mg/L)**	3.95 ± 0.05	3.53 ± 0.09	<0.001

1-hPG and 2-hPG: Oral glucose tolerance test 1 and 2 hour plasma glucose, **BMI:** body mass index, **eGFR:** estimated glomerular filtration rate, **FPG:** fasting plasma glucose, **HbA1c:** hemoglobin A1c, **HDL-c and nonHDL-c:** nonHDL-c=total cholesterol–HDL-c, high density lipoprotein cholesterol, **HOMA-IR:** homeostasis model of assessment, **hsCRP:** high sensitive C-reactive protein, **sBP and dBP:** systolic and diastolic blood pressure, **TG:** triglycerides, **WHR:** waist-to-hip ratio, *: Cockroft formula, **: ±Standard error of mean (SEM)

Table 2. Partial correlation analysis of hsCRP levels controlled for age, gender, urban/rural, and region with other parameters

	r	p
BMI	0.144	<0.001
Waist	0.129	<0.001
FPG	0.041	0.026
1-hPG	0.091	<0.001
2-hPG	0.088	<0.001
HDL-c	-0.076	<0.001
Fasting insulin	0.073	<0.001
HbA1c	0.083	<0.001
HOMA-IR	0.054	0.003
eGFR - Cockcroft	0.122	<0.001

1-hPG and 2-hPG: Oral glucose tolerance test 1 and 2 hour plasma glucose, **BMI:** body mass index, **eGFR:** estimated glomerular filtration rate, **FPG:** fasting plasma glucose, **HbA1c:** hemoglobin A1c, **HDL-c:** high density lipoprotein cholesterol, **HOMA-IR:** homeostasis model of assessment, **hsCRP:** high sensitive C-reactive protein, **sBP and dBP:** systolic and diastolic blood pressure.

Table 3. Ad hoc analysis of adjusted mean hsCRP levels across glucose tolerance groups

GT Status	GT Status	Mean Difference	p
NGT	i-IFG	-0.637	0.023
	i-IGT	-0.540	0.118
	CGI	-0.999	0.006
	new DM	-2.160	<0.001
	known DM	-1.119	0.002
i-IFG	NGT	0.637	0.023
	i-IGT	0.097	0.809
	CGI	-0.362	0.379
	new DM	-1.523	<0.001
	known DM	-0.482	0.243
i-IGT	NGT	0.540	0.118
	i-IFG	-0.097	0.809
	CGI	-0.459	0.314
	new DM	-1.620	0.001
	known DM	-0.578	0.204
new DM	NGT	2.160	<0.001
	i-IFG	1.523	<0.001
	i-IGT	1.620	0.001
	CGI	1.161	0.014
	known DM	1.042	0.026
known DM	NGT	1.119	0.002
	i-IFG	0.482	0.243
	i-IGT	0.578	0.204
	CGI	0.120	0.794
	new DM	-1.042	0.026

CGI: Combined glucose intolerance (IFG+IGT), **i-IFG:** isolated impaired fasting glucose, **i-IGT:** isolated impaired glucose tolerance, **GT status:** glucose tolerance status, **new DM:** newly diagnosed diabetes mellitus, **NGT:** normal glucose tolerance, **known DM:** previously diagnosed diabetes mellitus.

vigorously associated with individuals having CGI (IFG+IGT).[26] Also Doi *et al.* and Hashimoto *et al.* stated that concentration hsCRP related to 2-hPG rather than FPG in non-diabetic Japanese.[27,28] Results from different ethnic populations support that elevated hsCRP is linked with prediabetes.[25-31]

IFG and IGT represent two different concepts to develop DM with different pathophysiological mechanisms, the first is linked with IR at the liver level, and the latter is being related with peripheral IR. Approximately 30% to 40% individuals with IGT progresses to T2DM within 10 years of follow-up.[32] However, only a smaller part of the individuals with IFG will develop DM. In our study population, the mean concentrations of hsCRP in both IFG and IGT were higher than in normal but lower than in new-DM group. Moreover, the mean hsCRP in IFG group was numerically but not significantly higher than in IGT group. This might come from the concept that IFG is linked with elevated FPG, and since hsCRP is secreted from the liver, and might be produced more CRP during the IFG stage.[5,6]

The IRAS study and Aronson *et al.* revealed a negative correlation between hsCRP and HDL-c; this was confirmed in our study as well.[2,33] Lu *et al.* reported a strong correlation between HOMA-IR and hsCRP, independent of BMI and abdominal obesity in Asian patients with DM.[21] Studies have shown significant association between CRP levels and DM, it remained after adjusting for BMI or other covariates. In ADOPT study reported hsCRP levels in women were higher than in men in both with and without MS groups. They reported a positive correlation between hsCRP and HbA1c, BMI and HOMA-IR after the adjustments for age, gender and ethnicity. In addition, they found a vigorous correlation between the number of MS components and hsCRP in individual with newly diagnosed diabetes.[22]

One of the greatest strengths of the present study is its national representative sampling with a large sample size and wide age range. Furthermore, the large sample size of our study allowed us to examine simultaneously the association of hsCRP as an inflammatory marker with other biochemical parameters. The major limitations include the cross-sectional design and somewhat higher participation of women, which was controlled with large sample size.

Based on our study results, we stated that hsCRP might have an important role in development of diabetic process. The fact confirmed that any abnormality of the glucose tolerance (either pre-DM or DM) is associated with a low-grade inflammation. However, in established DM (previously diagnosed diabetes with longer

duration), the impact of inflammatory process may not be as strong as in the earlier metabolic derangements.

CONCLUSION

To our knowledge this is the largest study so far evaluating the association between subclinical inflammation and IR and all categories of glucose tolerance.

Part of the results might be confirmatory however the lack of difference between previously known DM and NGT status. Suggests that inflammation is actually an ongoing process but with long diabetes duration the contribution of inflammation might be rather small.

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Appendix - TURDEP-II Study Group

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*The authors declare that there are no conflicts of interest.

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