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ORIGINAL PAPER

The effect of omega 3 fatty acid supplementation on HbA1c serum in geriatric patients with type 2 diabetes mellitus: an evidence-based case report

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Abstract

Background: The prevalence of diabetes mellitus as a non-communicable diseases increase annually. The global prevalence doubled from 4.7% to 8.5% in 1980 until 2016. Insulin resistance is the primary cause of type 2 diabetes mellitus. Polyunsaturated fatty acid has a contribution to membrane fluidity as well as the cell signaling system. The result of studies about the correlation between Omega-3 supplementation and blood glucose control in patients with type 2 diabetes is still inconsistent. Meanwhile, we considered to give a 86 year old woman with an uncontrolled type 2 diabetes omega-3 fatty acid supplementation for controlling her blood glucose. Thus, we performed an evidence-based case report to respond this problem.

Objectives: To observe the effect of omega-3 supplementation on glycated hemoglobin (HbA1c) serum of type 2 diabetes mellitus patients.

Methods: Electronic literature searching was performed with Cochrane®, Scopus®, and Pubmed®. Inclusion and exclusion criteria were applied by MeSH term and title/abstract with clinical trial as the study design. Critical appraisal was performed for eligible article.

Results: There were three articles relevant with the eligibility criteria and clinical question. One study found that omega-3 supplementation did not give a significant effect on HbA1c. The other two studies. found that there were improvement on HbA1c and lipid profile in patients that consumed omega 3.

Conclusions: Omega-3 supplementation has inconsistent results for the improvement of HbA1c. The omega-3 lowering effect of HbA1c depends on the source, dosage, and duration of supplementation.

Keywords type 2 diabetes mellitus, omega-3 fatty acid, geriatric, HbA1c

Clinical scenario

An 86-year-old woman was admitted to the hospital with a chief complaint of decreased of appetite for three days before admission. She also complained cough and nausea with the absence of fever or vomiting. Her blood glucose level on the first day of care was 161 mg/dl. She was diagnosed with diabetes mellitus since two years ago and hypertension since seven years ago. She also has decreased kidney function since two years ago. She stopped taking oral hypoglycemic drugs since one year ago because of her daily blood glucose was within normal limits. Her blood glucose kept on increasing during the hospitalization that caused her to take oral hypoglycemic drugs to overcome her

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high blood glucose level. Her blood glucose on the second and third admission day reached 241 mg/dL despite her regular oral hypoglycemic drugs intake.

The physical examination revealed that this patient has an irregular heart beat. She was given enteral nutrition by nasogastric tube since the first day of admission. Her nutritional status was mild malnutrition with the body mass index of 18 kg/m^2. Clinical nutrition specialist planned to give her omega-3 supplementation to decrease HbA1c but whether omega-3 supplementation will give a significant effect on this patient was still on consideration.

Introduction

Diabetes is a chronic disease caused by the inability of the pancreas to produce insulin or insulin-resistant, manifested as high blood glucose level or hyperglycemia.[2,3] The prevalence of diabetes mellitus as one of non-communicable disease tend to increase annually.[3] The global prevalence of diabetes doubled since 1980 from 4,7% to 8,5% in 2016.[2] Diabetes prevalence in Indonesia is increased 1.7% from 2013 until 2018. [4]

Diabetes mellitus can be classified as type one and type two diabetes mellitus. Type two diabetes is more prevalent than type one diabetes mellitus.[2] Type two diabetes mellitus is caused by insulin-resistance that occur in the muscle and liver.[3] High-fat diet, especially saturated fat, will reduced insulin sensitivity that lead to insulin resistance.[5] On the other side, high polyunsaturated fat intake will improve insulin secretion and sensitivity. Physiologically, polyunsaturated fatty acid maintains the cell membrane fluidity to facilitate cell signaling pathway that augment insulin sensitivity. [6]

There are many literatures that report the correlation between omega-3 fatty acid supplementation and insulin resistance, but only a few that use HbA1c as a parameter of the study. It is still under debate, whether omega-3 supplementation increase insulin sensitivity in patients with type two diabetes mellitus. Various dosage regimen is one of the reason for this inconsistent result other than difference in length of supplementation.[7] Whether omega-3 supplementation has a positive effect on blood glucose management, observed with the HbA1c level in geriatric population as our patient suffered from, is an interesting field to study.

Clinical questions

The inclusion criteria for the subjects in this study are geriatric patients diagnosed with diabetes mellitus type 2. Glycate hemoglobin is the outcome of this study that compose the clinical question. The clinical question of this study: Can omega-3 supplementation reduce HbA1c levels in patients with diabetes mellitus type 2?

P : geriatric patients that is diagnosed to have diabetes mellitus type 2
I : omega-3 supplementation
C : placebo
O : HbA1c

Methods

Search Strategy

Advanced searching was used for this literature searching from three main databases: Pubmed®, Cochrane®, and Scopus® on December 19th, 2019. MesH Term and abstract/title was used as the searching criteria with the keywords of "omega 3 fatty acid", "alpha-linolenic acid", "HbA1c", "A1c", dan "diabetes mellitus". The result of this literature searching was then screened with EndNote™ application to eliminate duplication. Full text literatures which met the eligibility criteria and PICO were critically appraised.

Strategy of article selection

Eligibility Criteria

The articles were selected based on the inclusion and exclusion criteria, which is in line with the clinical question. The inclusion criteria were: 1) participants diagnosed as type 2 diabetes mellitus; 2) Geriatric patients (aged ≥60 years old); 3) Same characteristics subjects; 4) HbA1c measurement was done before and after intervention; 5) Randomized clinical trial 6) HbA1c as the study outcome and 7) publication within the last 5 years. The exclusion criteria were: 1) no available full text and 2) language other than English.

Critical appraisal

Critical appraisal was based on a therapy study, with HbA1c as the outcome measured. All of the relevant articles were assessed for validity, importance, applicability (VIA) with standardized critical appraisal for therapy study.

Results

A total of 793 articles were identified from Pubmed®, 13 from Cochrane®, and 43 from Scopus® based on keywords, MesH Terms, abstract/title (Table 1).

That literature was screened for titles that contain keywords listed. The result of the title screened was 15 relevant literatures that is eligible for the next screening step. All these relevant literature was screened for inclusion and exclusion criteria, 3 literatures fulfilled the eligibility criteria. Among 12 literatures that excluded, 10 literatures used outcome measure other than HbA1c and 2 literatures included Participants below 60 years of age. (Figure 1).

All of these three literatures used randomized double-blind controlled trials as their study design with a level of evidence of 2.The participants were diagnosed with diabetes and received omega-3 fatty acid. The HbA1c examination was performed to all the participants as one of their clinical outcomes. Study characteristics are shown in table 2. Zeng et al. almost fulfill all the appraisal criteria, followed by Wang et al. that did not fulfill two criteria, and Soleimani et al that did not fulfill three appraisal criteria.

Discussion

Soleimani et al.[10] conducted a randomized double-blind placebo-controlled clinical trial to 60 participants with diabetic foot ulcer grade 3 by Wagner-Meggit's criteria. Participants included in this study ranged from 40 years old until 85 years old. Participants were divided into two groups with one group was given omega-3 fatty acid from flaxseed oil 1 g/day for 12 weeks and the other one was given placebo both for 12 weeks. Participants were monitored during the 3rd week, 6th week, 9th week, and 12th week. The primary outcome of this study was wound healing and glucose homeostasis, the secondary outcome was lipid profile, inflammatory biomarker, and oxidative stress. The result of this study was the improvement of wound healing and reduction of insulin serum, HOMA-IR, and HbA1c, also an increase in QUICKI. The secondary outcome was reduction in hs-CRP but there is no significant difference in lipid profile between intervention and placebo group. Omega-3 from flaxseed oil 2 grams/day can reduce of HbA1c from baseline 7.5 +/- 1.5% compare to the end-of-trial 6.6 +/- 1.4% that change about -0.9 +/- 1.5%, (p=0.01).[10]

Wang F et al.[1] conducted a randomized, double-blind, placebo-controlled trial, to 100 participants age 65,4 +/- 5,3 years old diagnosed as type 2 diabetes mellitus and central obesity. Participants were divided into an intervention group that was given omega-3 from fish oil 4 grams/day that contains 1.34 g EPA and 1.07 g DHA compared with placebo for 6 months. Participants were monitored for their conformity monthly by returning the empty bottle that was filled by the omega-3 capsule before. The result of this study is that omega-3 fatty acid from fish oil was not significantly different compared with placebo in terms of HbA1 reduction with baseline 7.72 +/- 1.23%, 3rd month 7.85 +/- 1.55%, and 6th month 7.34 +/- 1.51% (p=0.901). There is a significant reduction in triglyceride (p=0,007) and increase in HDL (p=0,006) when compared to placebo in this study.[1]

A double-blind randomized controlled trial was conducted by Zheng J.S et al.[11] to 185 participants that were diagnosed with type 2 diabetes mellitus aged 35 until 80 years old. The participants were divided into three intervention groups that were fish oil group, flaxseed oil group, and corn oil group. All the participants were given capsules containing EPA and DHA 4 times a day for 180 days. Participants in the fish oil group were given 2 grams of omega-3 fatty acid containing EPA and DHA, meanwhile, participants in the flaxseed oil group received 2.5 grams of alpha-linolenic acid. Participants were monitored on the 90th day and 180th day by returning their omega-3 bottle. Trained nurses make a phone call once a month to make sure every participant consumed the omega-3 capsule that was given. The result of this study is that omega-3 fatty acid from fish oil reduced HbA1c better than flaxseed and corn

oil group (p=0,037). Triglyceride, low-density lipoprotein, and total cholesterol decreased more significantly in the fish oil group than the other groups ($p<0.05$). Flaxseed oil group and the corn oil group did not differ significantly.[11]

The HbA1c lowering effect of omega-3 fatty acid from study of Soleimani et al.[10] can be explained due to the effect of omega-3 fatty acid on modulating peroxisome proliferator-activated receptors and increasing gene expression of G protein-coupled receptor 120 that related to insulin metabolism.[10] Wang F et al.[1] found that there is no significant effect of omega-3 supplementation on HbA1c.[1] Difference between study results might be related to differences in sample size, source of omega-3 fatty acids, dosage of daily omega-3 supplementation, duration of supplementation, or participant disease characteristic.

Zheng J.S et al.[11] found that there are different effectivity of omega-3 fatty acids from different sources of omega-3 fatty acids such as fish oil, flaxseed oil, and corn oil. The result of this study explained that fish oil reduced HbA1c better than flaxseed oil and corn oil. Fish oil given in this study was 2 grams for 6 months.[11] Fish oil contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as compared to alpha-linolenic acid of flaxseed oil that need to be converted to EPA and DHA.[12]

In our case of geriatric 86 years old woman suffered from type 2 diabetes mellitus with increasing blood glucose during hospitalization. Her age and diagnosis are similar to these studies. We recommended on giving omega-3 fatty acids from 2 grams of fish oil daily besides continuous medical nutritional therapy to improve the patient's HbA1c.

Conclusions

The effect of omega-3 fatty acid to decrease HbA1c still has no consistent result. This can be explained by the difference in the dosage and duration of supplementation. Although there were still inconsistent results, 2 out of 3 literatures in this study conclude that omega-3 fatty acids give a significant effect on the reduction of HbA1c. Omega-3 fatty acids from fish oil give better effect when compared to omega-3 from flaxseed oil and corn oil for HbA1c and lipid profile improvement. The effect of omega-3 fatty acid for HbA1c reduction depends on the source, dosage, and duration of supplementation. The limitation of this study are no precise dosage and explanation whether age will affect the result of the study, there is no study that explain whether different age population will give different response to omega-3 supplementation. Further research is needed to confirm the effect of omega-3 supplementation on HbA1c.

Table 1. Resources & search strategy

Database	Search Strategy	Hits	Choosen
Pubmed	(((((((((omega 3 fatty acids[MeSH Terms]) OR omega 3 fatty acids[Title/Abstract]) OR alpha linolenic acid[MeSH Terms]) OR alpha linolenic acid[Title/Abstract]) AND hb a1c[MeSH Terms]) OR hb a1c[Title/Abstract]) OR A1c[MeSH Terms]) OR A1c[Title/Abstract]) AND diabetes mellitus[MeSH Subheading]) OR diabetes mellitus[Title/Abstract]	**793**	**4**
Cochrane Library	ID Search Hits #1("omega 3 fatty acids"):ti,ab,kw 2010 #2 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees 2923 #3("alpha-linolenic acid"):ti,ab,kw 0 #4MeSH descriptor: [alpha-Linolenic Acid] explode all trees 226 #5("Hb A1C values"):ti,ab,kw 374 #6 MeSH descriptor: [Glycated Hemoglobin A] explode all trees 5458 #7("glycated haemoglobin levels"):ti,ab,kw 191 #8 MeSH descriptor: [Glycated Hemoglobin A] explode all trees 5458 #9("diabetes mellitus"):ti,ab,kw 59410 #10 MeSH descriptor: [Diabetes Mellitus] explode all trees 28035 #11#1 OR #2 OR #3 OR #4 4317 #12#5 OR #6 OR #7 OR #8 5851 #13#9 OR #10 62938 #14#11 AND #12 AND #13 with Cochrane Library publication date Between Jan 2017 and Dec 2019, in Trials 13	**13**	**6**
Scopus	(TITLE-ABS-KEY (omega 3 fatty AND acids) OR TITLE-ABS KEY (alpha AND linolenic AND acid) AND TITLE-ABS-KEY (hb AND a1c) OR TITLE-ABS-KEY (a1c) AND TITLE-ABS-KEY (diabetes AND mellitus)) AND DOCTYPE (ar) AND PUBYEAR > 2016 AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-TO (EXACTKEYWORD , "Human")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SRCTYPE , "j"))	**43**	**5**

Table 2. Study characteristics

Articles	Study design	Intervention	Population	Outcome
Soleimani Z et al. (2017)	A randomized, double-blind, placebo-controlled trial	Flaxseed oil 1 grams/day for 12 week compared with placebo	60 patients, 45-80 years old diagnosed with grade 3 diabetic foot ulcer grade 3 (Wagner-Meggitt's criteria) with cellulitis and normal distal pulse.	Wound healing, glucose homeostasis parameter (serum insulin concentration, homeostasis model of assessment-insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), Hemoglobin A1c (HbA1c), and fasting plasma glucose), and lipid profiles.
Wang F et al., (2017)	A randomized, double-blind, placebo-controlled trial	Fish oil 4 grams/day compared with placebo for 6 month	100 Participants, >60 years old diagnosed with type 2 diabetes by World Health Organization (WHO) criteria and abdominal obesity by Working Group on Obesity of China (WGOC) criteria.	Waistline, hipline, height, systolic and diastolic blood pressure, serum fatty acid composition and body composition, body composition, serum glucose, HbA1c, insulin, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).
Zeng J.S et al., (2016)	Double-blind randomized controlled trial	Fish oil 2 grams/day, flaxseed oil 2.5 grams/day.	185 Participants, 35-80 years old for men and between post-menopausal age until 80 years old for woman. Fasting blood glucose >7.0 mmol/L or use of diabetic medications.	Fasting blood glucose, HDL-C, LDL-C, total cholesterol, TG, glucose, uric acid, blood urea nitrogen (BUN), creatinine, liver function markers, blood total protein, globulin (GLB), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IDBIL), HOMA-IR, HbA1c

ALB: albumin, BUN: blood urea nitrogen, DBIL: direct bilirubin, IDBIL: indirect bilirubin, GLB: globulin, HbA1c: hemoglobin A1c, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein, HOMA-IR: homeostasis model of assessment-insulin resistance, TBIL: total bilirubin, TC: total Cholesterol TG: triglyceride, QUICKI: quantitative insulin sensitivity check index,

Table 3. Validity criteria

Validity						Relevance			
Articles	Randomization	Same characteristic	Same treatment	*Intention to treat*	*Blinded* / objective	Applicability	Clinically important	Result	Level of Evidence[9]
Soleimani et al[10]	+	+	+	+	+	-	-	A	2
Wang Fet al[1]	+	+	+	-	+	+	-	B	2
Zheng, J.S et al[11]	+	+	+	?	+	+	+	C	2

A: Significant reduction of HbA1c in the intervention group ($p=0.01$)[10]
B: Reduction of HbA1c did not differ significantly between the intervention group and placebo group ($p>0.05$).[1]
C: HbA1c significantly decreased statistically in the fish oil group compared with the flaxseed oil and corn oil group ($p<0,001$).[11]

Table 4. Relevance criteria

	Similarity Population	Similarity Determinant	Similarity Outcome
Soleimani et al[10]	+	+	+
Wang F et al[1]	-	+	+
Zheng J.S et al[11]	+	+	+

Table 5. Result of studies

Articles	Outcome	Key Results
Soleimani Z, Hashemdokht F, Bahmani F, Taghizadeh M, Memarzadeh MR, Asemi Z. (2017) *Journal of Diabetes and Its Complications*[10]	• Wound healing • Serum insulin, homeostasis model of assessment-estimated insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), HbA1c. • Lipid profile: triglyceride, VLDL, LDL, HDL • Inflammation marker: high sensitivity C-reactive protein (hs-CRP), nitric oxide, total antioxidant capacity (TAC), glutathione total (GSH), dan malondialdehyde (MDA)	• The reduction in wound size is more significant in 12 weeks omega-3 supplemented participants • The reduction of insulin concentration, HOMA-IR, and HbA1c is statistically significant. • The result for HbA1c: baseline 7.5 +/- 1.5%, end-of-trial 6.6 +/- 1.4%, change -0.9 +/- 1.5%, p=0.01 • The increase in QUICKI is also statistically significant
Wang F, Wang Y, Zhu Y, et al. (2016), *European Journal of Nutrition*[10]	• Fasting blood glucose, HbA1c, insulin, HOMA- • Lipid profile such as triglyceride, LDL, HDL	• Omega-3 supplementation for 12 weeks reduced triglyceride level significantly (P=0,007) • Omega-3 supplementation were not statistically significant in affecting HOMA-IR, fasting blood glucose, and HbA1c • The result for HbA1c baseline was 7.72 +/- 1.23%, 3 months 7.85 +/- 1.55%, 6 months 7.34 +/- 1.51%, p=0.901
Zheng JS, Lin M, Fang L,(2016), *Molecular Nutrition & Food Research Journal*[11]	• Fasting blood glucose, fasting plasma insulin, HOMA-IR, HbA1c. • HDL, LDL, triglyceride, and total cholesterol • BUN, creatinine, uric acid, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, total protein, globulin, and albumin.	• Omega-3 fatty acid from fish oil gives a better statistically significant effects on glycemic control and lipid profile compared with flaxseed oil and corn oil. • HbA1c reduction is statistically significant in fish oil group compared with flaxseed and corn oil. (on day 0: 63.9 +/- 22.9 mmol/mol, on day 90th: 52.7 +/- 13.8 mmol/mol, on day 180th: 54.4 +/- 13.4 mmol/mol, p=0.035)

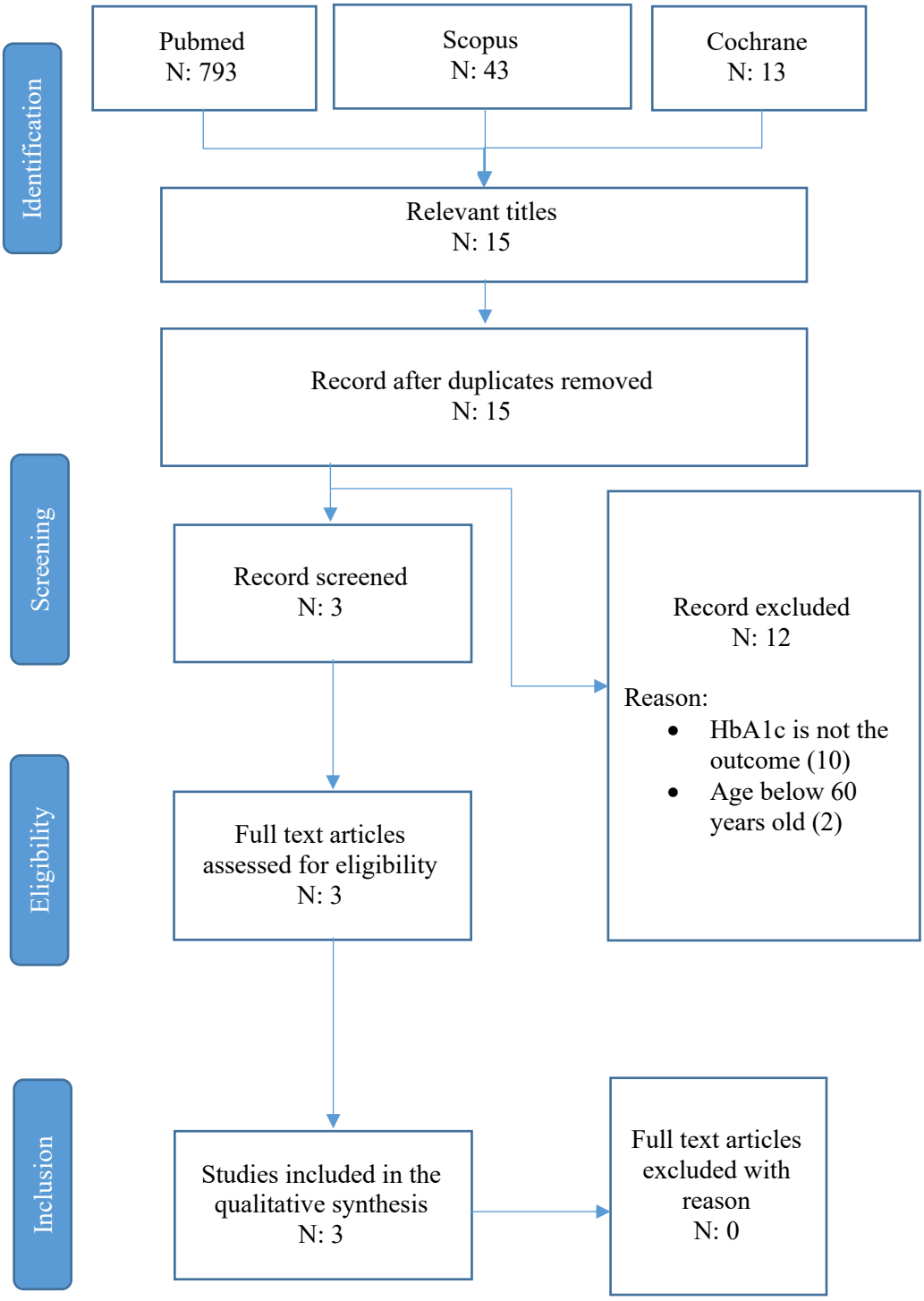

Figure 1. Prima's flow chart of literature searching

Conflict of interest

The authors declare no conflict of interest regarding this study.

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