DETERMINATION OF THE RELATIONSHIP OF VISPHATIN AND HOMOCYSTEINE LEVELS WITH INDICATORS OF GLUCOSE METABOLISM AND LIPID METABOLISM IN PERI- AND POSTMENOPAUSE WOMEN WITH TYPE 2 DIABETES MELLITUS AND OSTEOARTHRITIS

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Abstract

Type 2 diabetes mellitus (T2DM), among other modern diseases, certainly occupies a leading position today. Moreover, the comorbid combination of T2DM and osteoarthritis (OA) is a common example of the development of complications, disability and mortality these days. As you know, T2DM develops against the background of obesity and overweight. A significant group of patients prone to these pathologies are peri- and postmenopausal women. Estrogen deficiency during this period worsens the course of these interdependent conditions. Therefore, searching for ways of early diagnosis of OA in women with T2DM is an urgent task of internal medicine.

Purpose. To determine the interdependencies of indicators of glucose metabolism and lipid metabolism with levels of visfatin (VF) and homocysteine (HC) in women with T2DM and OA in peri- and postmenopause.

Methods. For the study, 120 thematic women in peri- and postmenopause were selected and were divided into three groups: 1st (n = 20) – women with a mono-course of T2DM; 2nd (n = 20) – with a mono-course of OA; 3rd (n = 64) – with the comorbid course of T2DM and OA. The control group (CG) consisted of 16 relatively healthy women of the appropriate age. Diagnoses of T2DM and OA were established in accordance with the current Orders of the Ministry of Health of Ukraine. Laboratory diagnostic methods were performed according to standard methods.

The results. According to the obtained results, the presence of interdependencies of all indicators of lipid metabolism and glucose-insulin metabolism was reliably determined, which indicated direct correlations (mostly of moderate strength) with the levels of HC and VF in the blood of the examinees, most pronounced in the comorbid combination of T2DM and OA in peri- and postmenopause.

Conclusions. In work, an analysis of the correlations of indicators of glucose metabolism and lipid metabolism with disturbances in the metabolism of VF and HC in women with T2DM and OA in pre- and postmenopause was carried out, and their interdependent relationships were determined. The highest levels of VF and HC were recorded in the group of women with comorbid pathology of T2DM and OA.

Keywords: type 2 diabetes mellitus, osteoarthritis, visfatin, homocysteine, women, perimenopause, postmenopause, metabolism.

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1. Introduction

According to official statistics [1–3] and the results of many studies, the global prevalence of diabetes mellitus (DM) is noted at levels higher than 463 million patients, of which a significant part (more than 90.0 %) has type 2 DM [4]. In Ukraine, according to data from 2016 [5], a significant (by 5.0–7.0 %; more than 3.5 million people) [6] annual increase in the level of diabetes is also constantly recorded, almost reaching the European average (9.1 %) [7] of DM prevalence levels (87.0–91.0 % – type 2 DM [7, 8]).

Researchers also associate significant negative medical and social consequences with significant comorbidity of type 2 diabetes [9]. Scientists [10] explain high levels of comorbidity with similar etiological factors (obesity, increased body mass index (BMI), impaired carbohydrate

metabolism, endothelial dysfunction) [11]. Among such diseases, cardiovascular nosology, diseases of the gastrointestinal tract, joints, thyroid gland, lungs, and others are primarily distinguished. So, AlvaP et al. [12, 13] indicate a significant interdependence of type 2 diabetes with obesity and BMI, which is especially characteristic of the female cohort [14] due to hormonal changes during peri- and postmenopause (with BMI 25 < 30 kg/m^2 in women AlvaP et al. noted increased risks of occurrence and development of type 2 diabetes). Other studies [13, 15–20] conducted in the USA note the interdependence of 90.0–95.0 % of all cases of type 2 diabetes with obesity. At the same time, many scientists also point to a significant list of comorbidities with increased BMI and type 2 diabetes, among which OA is quite common, the development of which is fully associated with increased BMI and the duration of obesity due to common risk factors (primarily age characteristics, obesity, dyslipidemia) [21] and loss of estrogen in women during peri- and postmenopause [22]. MahajanA and PatniR indicate that the risks of OA are maximally high after the onset of menopause in women and are 3.5 times higher than the corresponding risks among men aged 50–60 years [23]. Other studies (WuJ. H. et al. [24]) reliably ($p < 0.05$) prove high relationships between type 2 diabetes and OA, especially for women of postmenopausal age (it is determined that OA in type 2 diabetes typically occurs in 32.65 % of cases and occurs mostly in women (38.05 %), compared to men (27.41 %)) [25]. When women lose estrogen, the so-called metabolic syndrome occurs [26], the severity of which is completely interdependent with adiposity (especially visceral) and BMI It should be noted that a significant number of studies indicate high correlations of metabolic syndrome, visceral adiposity and BMI with insulin resistance and type 2 DM [27] through specific adipocytokines [28–29].

In a number of works, there are data on the relationship between obesity and type 2 diabetes with increased levels of visfatin (VF) in the blood [30–37]. However, studies investigating the clinical value of visfatin in postmenopausal women with comorbid pathology are rare. Other studies conducted indicate a probable relationship between OA risk factors (obesity, presence of type 2 diabetes, insulin resistance) with increased levels of homocysteine (HC) [38–40] and the presence of metabolic syndrome in peri- and postmenopausal women [14].

At the same time, elevated blood HC levels are probably associated with the presence of atherosclerosis, OA, type 2 diabetes, and cardiovascular diseases [41–46]. Hyperhomocysteinemia is completely associated with the effect on osteoclasts and osteoblasts, which provokes a significant decrease in bone strength and the development of OA [47].

Taking into account the above, we determined **the main aim of the work**: to analyze the correlational interdependencies of indicators of glucose metabolism and lipid metabolism with VF and HC metabolism disorders in women with type 2 diabetes and OA in peri- and postmenopause.

2. Materials and methods

The main group of studied patients consisted of women who were treated in the rheumatology and endocrinology departments of the CE KRC CHOR «RCH» in 2018–2019, which is the clinical base of the Department of Internal Medicine No. 3 and Endocrinology of the Kharkiv National Medical University.

To conduct the study, we selected a group of 120 peri- and postmenopausal women, who were divided into three groups; 1st (n = 20) – women with a mono-course of type 2 diabetes; 2nd (n = 20) – with a mono-course of OA; 3rd (n = 64) – with the comorbid course of type 2 DM and OA. The control group (CG) consisted of 16 relatively healthy women of the appropriate age.

All women signed informed consent for their involvement in the study in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The conduct of the study was approved by the decision of the Committee on Ethics and Bioethics of the Kharkiv National Medical University (protocol No. 8 dated October 3, 2018).

The diagnosis of type 2 diabetes was established in accordance with the generally accepted criteria in clinical practice and the order of the Ministry of Health of Ukraine No. 1118 dated 21.12.2012. The diagnosis of OA was established in accordance with the order of the Ministry of Health of Ukraine, «Clinical protocol for providing medical care to patients with osteoarthritis (OA)», No. 676 dated October 12, 2006. The presence of menopause was confirmed by

a gynaecologist's consultation (including the determination of FSH levels according to the STRAW10+ classification). Decreased levels of estradiol in the blood serum of the examined women were ascertained in the laboratory.

The height and weight of the examinees were measured with a floor scale with RPV-2000 «Primed» scales. BMI was determined by the formula: body weight (in kg) divided by the square of the patient's height (in m^2). To determine the levels of VF and HC in blood, a variant of indirect non-competitive heterogeneous enzyme immunoassay was used on the analyzer «Labline-90» (Austria) using a commercial test system manufactured by the company «Elabscience» (China).

To assess carbohydrate metabolism, fasting blood glucose (FBG) was determined. The concentration of immunoreactive insulin (IRI) in the fasting state was determined by the immunoenzymatic method. The HOMA index was calculated mathematically according to the formula: HOMA-IR = IRI (μU/ml) * FBG (mmol/l)/22.5. Glycemic profile data were evaluated per day (at 6:00 a.m., 12:00 p.m. and 9:00 p.m.).

The state of lipid metabolism was assessed by the content of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), high-density lipoprotein (HDL) using an enzymatic method using standard kits. The atherogenic coefficient (AC) was calculated mathematically according to the formula: AC = (TC–HDL)/HDL.

Statistical processing. Statistical processing of the obtained data was carried out using the statistical data processing program package version 21 «IBM SPSS Statistics 21» (Statistical Product and Service Solutions – SPSS). The relationship between the obtained characteristics was determined using the Spearman rank correlation coefficient Rho (Spearman rank correlation R). If Rho was in the range from 0 to –1.0, the correlation was considered inverse; if from 0 to 1.0 – a straight line. Rho coefficients from 0 to 0.3 (from 0 to –0.3) stated the presence of a weak connection between the investigated characteristics; from 0.4 to 0.7 (from –0.4 to –0.7) – moderate strength and from 0.7 to 1.0 (from –0.7 to –1.0) – high strength. The result was presented in the form of the value of the Rho coefficient and the corresponding confidence level p. To analyze the levels of correlational interdependencies, all examined women of pre- and postmenopausal age (82 people) were divided into two main groups: 20 patients with an isolated course of type 2 diabetes (58.6 ± 7.1 years) and 62 women with the comorbid course of type 2 diabetes and OA (59.7 ± 4.0 years).

3. Research results

Based on the obtained results of lipid metabolism indicators in women with type 2 diabetes mellitus and OA, significant levels of the interdependence of all lipid metabolism indicators were determined: TC, TG, HDL and LDL, as well as VLDL and AC, which indicated direct correlation relationships (in most of the moderate strength) with the levels of HC and VF in the blood of the examinees (more prominent in the comorbid combination of type 2 diabetes and OA) – **Tables 1, 2, 3, 4**.

Thus, for women with a mono-course of type 2 diabetes, it was determined the presence of probable direct average strength of relationships between VF blood levels and HC ($\rho = 464$; $p = 0.049$), TC ($\rho = 0.481$; $p = 0.044$), TG ($\rho = 0.568$; $p = 0.007$), LDL ($\rho = 0.510$; $p = 0.045$), VLDL ($\rho = 0.438$; $p = 0.031$) and AC ($\rho = 0.345$; $p = 0.050$) – **Table 1**. At the same time, a direct probable weak relationship was recorded with HDL levels ($\rho = 0.215$; $p = 0.036$). It should be noted that for the levels of HC in women with type 2 diabetes, almost all correlation levels were of medium strength and somewhat fewer probable interdependencies. Thus, HC levels were correlated with TC ($\rho = 0.345$; $p = 0.050$), TG ($\rho = 0.322$; $p = 0.051$), HDL ($\rho = 0.227$; $p = 0.010$), LDL ($\rho = 0.348$; $p = 0.040$), VLDL ($\rho = 0.321$; $p = 0.030$) and AC ($\rho = 0.259$; $p = 0.027$) – **Table 1.**

It was established that in the mono-course of type 2 diabetes, VF was probably directly weakly and at the lower limit of the average strength of interdependencies correlated with the NOMA index ($\rho = 0.219$; $p = 0.018$), insulin and HbA_{1c} levels (respectively $\rho = 0.379$; $p = 0.049$ and $\rho = 0.147$; $p = 0.045$) and glucose indicators at 6:00 a.m., 12:00 p.m. and 9:00 p.m. (respectively $\rho = 0.291$; $p = 0.019$; $\rho = 0.323$; $p = 0.057$ and $\rho = 0.279$; $p = 0.051$) – **Table 2**.

It should be noted that the HC levels showed in the vast majority direct weak correlations with indicators of glucose-insulin metabolism in the mono-course of type 2 diabetes: with the

NOMA index (ρ = 0.280; ρ = 0.046), levels of insulin and HbA_{1c} (respectively ρ = 0.296; p = 0.005 and ρ = 0.288; p = 0.012) and glucose levels at 6:00 a.m., 12:00 p.m. and 9:00 p.m. (respectively ρ = 0.254; p = 0.051; ρ = 0.291; p = 0.037 and ρ = 0.202; p = 0.039) – **Table 2.**

Table 1
Correlation relationships of VF and HC with indicators of lipid metabolism in women with isolated type 2 diabetes (n = 20)

Indicators		VF, ng/ml	HC, mmol/l	TC, mmol/l	TG, mmol/l	HDL, mmol/l	LDL, mmol/l	VLDL, mmol/l	AC
VF, ng/ml	ρ	1.000	0.464	0.481	0.568	0.215	0.510	0.438	0.345
	r	–	0.049	0.044	0.007	0.036	0.045	0.031	0.050
HC, mmol/l	ρ	0.464	1.000	0.345	0.322	0.227	0.348	0.321	0.259
	r	0.049	–	0.050	0.051	0.010	0.040	0.030	0.027
TC, mmol/l	ρ	0.481	0.345	1.000	0.145	–0.169	0.325	0.178	0.342
	r	0.044	0.050	–	0.541	0.477	0.162	0.452	0.140
TG, mmol/l	ρ	0.568	0.322	0.145	1.000	–0.837	0.153	0.260	0.638
	r	0.007	0.051	0.541	–	0.000	0.519	0.268	0.002
HDL, mmol/l	ρ	0.215	0.227	–0.169	–0.837	1.000	0.076	–0.100	–0.483
	r	0.036	0.010	0.477	0.000	–	0.750	0.675	0.031
LDL, mmol/l	ρ	0.510	0.348	0.325	0.153	0.076	1.000	0.484	0.436
	r	0.045	0.040	0.162	0.519	0.750	–	0.031	0.054
VLDL, mmol/l	ρ	0.438	0.321	0.178	0.260	–0.100	0.484	1.000	0.585
	r	0.031	0.030	0.452	0.268	0.675	0.031	–	0.007
AC	ρ	0.345	0.259	0.342	0.638	–0.483	0.436	0.585	1.000
	r	0.050	0.027	0.140	0.002	0.031	0.054	0.007	–

Table 2
Correlation of VF and HC with indicators of glucose-insulin metabolism in women with isolated type 2 diabetes (n = 20)

Indicators		HOMA index	Insulin, mU/ml	HbA_{1c}, %	Glucose 6.00, mmol/l	Glucose 12.00, mmol/l	Glucose 21.00, mmol/l
VF, ng/ml	ρ	0.219	0.379	0.147	0.291	0.323	0.279
	r	0.018	0.049	0.045	0.019	0.057	0.051
HC, mmol/l	ρ	0.280	0.296	0.288	0.254	0.291	0.202
	r	0.046	0.005	0.012	0.051	0.037	0.039
HOMA index	ρ	1.000	0.786	0.262	0.560	0.007	0.139
	r	–	0.000	0.265	0.010	0.977	0.560
Insulin, mU/ml	ρ	0.786	1.000	0.165	0.002	0.028	0.158
	r	0.000	–	0.488	0.995	0.907	0.505
HbA_{1c}, %	ρ	0.262	0.165	1.000	0.222	0.310	-0.357
	r	0.265	0.488	–	0.346	0.184	0.122
Glucose 6.00, mmol/l	ρ	0.560	0.002	0.222	1.000	0.041	0.120
	r	0.010	0.995	0.346	–	0.865	0.614
Glucose 12.00, mmol/l	ρ	0.007	0.028	0.310	0.041	1.000	0.004
	r	0.977	0.907	0.184	0.865	–	0.987
Glucose 21.00, mmol/l	ρ	0.139	0.158	–0.357	0.120	0.004	1.000
	r	0.560	0.505	0.122	0.614	0.987	–

Table 3

Correlation relationships of VF and HC with indicators of lipid metabolism in women with the comorbid course of type 2 diabetes and OA (n = 62)

Indicators		VF, ng/ml	HC, mmol/l	TC, mmol/l	TG, mmol/l	HDL, mmol/l	LDL, mmol/l	VLDL, mmol/l	AC
VF, ng/ml	ρ	1.000	0.468	0.560	0.577	0.327	0.573	0.569	0.403
	r	–	0.012	0.013	0.028	0.029	0.054	0.045	0.042
HC, mmol/l	ρ	0.468	1.000	0.465	0.402	0.306	0.390	0.406	0.306
	r	0.012	–	0.016	0.015	0.012	0.048	0.012	0.041
TC, mmol/l	ρ	0.560	0.465	1.000	0.359	–0.351	0.401	0.323	0.438
	r	0.013	0.016	–	0.004	0.005	0.001	0.010	0.000
TG, mmol/l	ρ	0.577	0.402	0.359	1.000	–0.715	0.247	0.472	0.471
	r	0.028	0.015	0.004	–	0.000	0.053	0.000	0.000
HDL, mmol/l	ρ	0.327	0.306	–0.351	–0.715	1.000	–0.274	–0.388	–0.592
	r	0.029	0.012	0.005	0.000	–	0.031	0.002	0.000
LDL, mmol/l	ρ	0.573	0.390	0.401	0.247	–0.274	1.000	0.679	0.699
	r	0.054	0.048	0.001	0.053	0.031	–	0.000	0.000
VLDL, mmol/l	ρ	0.569	0.406	0.323	0.472	–0.388	0.679	1.000	0.668
	r	0.045	0.012	0.010	0.000	0.002	0.000	–	0.000
AC	ρ	0.403	0.306	0.438	0.471	–0.592	0.699	0.668	1.000
	r	0.042	0.041	0.000	0.000	0.000	0.000	0.000	–

It is noted that with the comorbid combination of type 2 diabetes and OA, slightly higher probable levels of correlation interdependencies with indicators of lipid metabolism were recorded – **Table 3**. So, VF was reliably directly correlated with average strength with the levels of HC (ρ = 0.468; p = 0.012), TC (ρ = 0.560; p = 0.013), TG (ρ = 0.577; p = 0.028), HDL (ρ = 0.327; p = 0.029), LDL (ρ = 0.573; p = 0.054) and VLDL (ρ = 0.569; p = 0.045) and AC (ρ = 0.403; p = 0.042) – **Table 3**.

At the same time, blood HC levels determined slightly lower probable average correlation levels of interdependencies with indicators of lipid metabolism in women with type 2 diabetes and OA. Thus, HC was probably directly correlated with the average strength with the levels of TC (ρ = 0.465; p = 0.016), TG (ρ = 0.402; p = 0.015), HDL (ρ = 0.306; p = 0.012), LDL (ρ = 0.390; p = 0.015). p = 0.048), VLDL (ρ = 0.406; p = 0.012) and AC (ρ = 0.306; p = 0.041) – **Table 3**.

It should be noted that similar trends regarding the presence of direct (mostly weak) probable interdependencies were also established for the levels of VF, HC and indicators of glucose-insulin metabolism (NOMA index (insulin resistance index), levels of insulin and glycosylated haemoglobin (HbA_{1c}) and glucose indicators), more pronounced in the comorbid combination of type 2 diabetes and OA – **Tables 2, 4**.

With a comorbid combination of type 2 DM and OA, significantly larger (mostly of medium strength) probable direct correlations of VF and HC with indicators of lipid metabolism of the subjects were noted. Thus, VF established direct correlations of mostly medium strength with the NOMA index (ρ = 0.300; p = 0.040), levels of insulin and glycosylated haemoglobin (respectively ρ = 0.395; p = 0.046 and ρ = 0.215; p = 0.009) and levels glucose at 6.00, 12.00 and 21.00 (respectively, ρ = 0.374; ρ = 0.056; ρ = 0.420; ρ = 0.037 and ρ = 0.343; ρ = 0.042) – **Table 4.**

At the same time, blood HC levels with slightly lower correlation coefficients were interrelated with indicators of lipid metabolism of patients: with the NOMA index (ρ = 0.290; p = 0.022), levels of insulin and glycosylated haemoglobin (respectively ρ = 0.362; p = 0.027 and ρ = 0.331; p = 0.058) and glucose levels at 6:00 a.m., 12:00 p.m. and 9:00 p.m. (respectively ρ = 0.364; ρ = 0.021; ρ = 0.335; ρ = 0.057 and ρ = 0.243; ρ = 0.053) – **Table 4.**

Table 4

Correlation relationships of VF and HC with indicators of glucose-insulin metabolism in women with the comorbid course of type 2 diabetes and OA (n = 62)

Indicators		HOMA index	Insulin, mU/ml	HbA_{1c}, %	Glucose 6.00, mmol/l	Glucose 12.00, mmol/l	Glucose 21.00, mmol/l
VF, ng/ml	ρ	0.300	0.395	0.215	0.374	0.420	0.343
	r	0.040	0.046	0.009	0.056	0.037	0.042
HC, mmol/l	ρ	0.290	0.362	0.331	0.364	0.335	0.243
	r	0.022	0.027	0.058	0.021	0.057	0.053
HOMA index	ρ	1.000	0.846	0.338	0.388	0.244	0.122
	r	–	0.000	0.007	0.002	0.056	0.344
Insulin, mU/ml	ρ	0.846	1.000	0.190	0.081	0.016	0.027
	r	0.000	–	0.139	0.533	0.900	0.836
HbA_{1c}, %	ρ	0.338	0.190	1.000	0.802	0.740	0.614
	r	0.007	0.139	–	0.000	0.000	0.000
Glucose 6.00, mmol/l	ρ	0.388	0.081	0.802	1.000	0.856	0.648
	r	0.002	0.533	0.000	–	0.000	0.000
Glucose 12.00, mmol/l	ρ	0.244	0.016	0.740	0.856	1.000	0.728
	r	0.056	0.900	0.000	0.000	–	0.000
Glucose 21.00, mmol/l	ρ	0.122	0.027	0.614	0.648	0.728	1.000
	r	0.344	0.836	0.000	0.000	0.000	–

4. Discussion of the obtained results

The results obtained by the study are fully confirmed by other studies that indicate a fairly close relationship between insulin resistance and type 2 diabetes [25] through VF [26, 28] and HC [30] and the development of OA [47]. Other studies indicate likely interdependencies of increased levels of insulin, HC, and TG [30] and a significant effect of homocysteinemia on osteoclasts and osteoblasts (which provoke the development of OA) [47]. The similarity of the results is emphasized by the studies of HindyG. et al., who noted the presence of probable inverse correlations between LDL and OA risks (odds ratio (OR) = 0.83; 95.0 % CI 0.73–0.95 [48] and conclusions of TsiklauriL. et al. [49] and ÇıkımG. With VeranyurtÜ. [50], which indicated the presence of probable direct interdependencies between increased levels of VF and GM in OA (respectively 2.25 ± 0.36; $p = 0.002$ and 18.04 ± 8.44; $p < 0.05$).

Limitations of the study. It can be assumed that due to the limited number of women involved in the study and the quantitatively small availability of observations in each of the studied groups, the obtained data may differ slightly with further observations with improved monitoring. It should be noted that concomitant diseases in the studied women, such as oncological and acute inflammatory diseases, as well as taking hormone replacement therapy (which was an exclusion criterion in our study), may affect the results.

Prospects for further research. In further studies it is planned to determine the prognostic significance of VF and HC in the development of OA in pre- and postmenopausal women with type 2 diabetes with the construction of a model for early prediction of the development of OA in peri- and postmenopausal women with type 2 diabetes.

5. Conclusions

Thus, when analyzing the correlations of the indicators of glucose metabolism and lipid metabolism with VF and HC metabolism disorders in women with type 2 diabetes and OA in pre- and postmenopause, it was reliably determined:

1. The highest levels of VF and HC were noted in the group of comorbid pathology of type 2 diabetes and OA in peri- and postmenopausal women.

2. The presence of probable direct average strength of relationships between VF blood levels and HC, TC, TG, LDL, VLDL and AC for women with a mono-course of type 2 diabetes were recorded.

3. Somewhat higher probable levels of correlation interdependencies with indicators of lipid metabolism were determined in the case of a comorbid combination of type 2 diabetes and OA (VF was reliably directly correlated with average strength with the levels of HC, TC, TG, HDL, LDL, VLDL, and AC).

4. Levels of blood HC determined slightly lower probable average correlation levels of interdependencies with indicators of lipid metabolism in women with type 2 diabetes and OA.

5. In the case of a comorbid combination of type 2 diabetes and OA, probable direct correlations of VF and HC with indicators of lipid metabolism of the subjects were noted, mostly of medium strength. At the same time, blood HC levels were interrelated with indicators of lipid metabolism of patients: with NOMA index, levels of insulin and glycosylated haemoglobin, and glucose levels at 6:00 a.m., 12:00 p.m., and 9:00 p.m.

Conflict of interest

The authors declare that there is no conflict of interest in relation to this paper, as well as the published research results, including the financial aspects of conducting the research, obtaining and using its results, as well as any non-financial personal relationships.

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Data availability

The manuscript has associated data in a data repository.

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