



ORIGINAL ARTICLE

Effects of regular physical exercise on skin blood flow and cardiovascular risk factors in overweight and obese subjects

Efeitos do exercício físico regular sobre o fluxo sanguíneo da pele e nos fatores de risco cardiovascular em indivíduos com sobrepeso e obesidade

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Abstract

Objective: it is well known that low omentin levels and reduced bioavailability of nitric oxide (NO) are outgrowth of obesity. Besides, in obese subjects, microvascular dysfunction can be an initial stage of cardiovascular diseases. This situation can be evaluated with skin laser-Doppler flowmetry (LDF).

Methods: in this study we investigated the effects of 12 weeks moderate physical exercise on microvascular reactivity and plasma levels of omentin and NO in 25 overweight and obese subjects. Control group was composed of 28 sedentary participants who were neither obese nor overweight. Microvascular reactivity was handled by measurement of skin blood flow from the ring finger of the right hand with LDF, which is a non-invasive method for evaluation. With this method, it was aimed to examine the post-occlusive reactive hyperemia response of the patients. None of the participants in both groups have never followed a regular exercise schedule in their life span.

Results: with regular exercise, there was a statistically significant decrease in glucose ($p=0.008$), cholesterol ($p=0.05$), and triglyceride ($p=0.048$) levels, while body mass index, high-density lipoprotein, and low-density lipoprotein levels did not change significantly in overweight/obese group. Also, the omentin level significantly increased ($p=0.01$), but NO level did not change significantly. Moreover, the amount of change in omentin and NO levels measured before and after the physical exercise were significantly correlated ($r=0.57$). Considering the microcirculation, rest flow ($p=0.001$) and peak flow value of LDF ($p=0.001$) increased after the physical exercise.

Conclusion: our study shows that moderate physical exercise affects microvascular reactivity and plasma levels of omentin in overweight and obese subjects.

Keywords: laser-doppler flowmetry, nitric oxide, omentin, obesity, physical exercise.

Resumo

Objetivo: sabe-se que níveis baixos de omentina e a reduzida biodisponibilidade de óxido nítrico (NO) são consequências da obesidade. Além disso, a disfunção microvascular pode ser um estágio inicial de doenças cardiovasculares em indivíduos obesos. Essa situação pode ser avaliada com a fluxometria de pele laser-Doppler (LDF).

Métodos: foram investigados os efeitos do exercício físico moderado por 12 semanas na reatividade microvascular e nos níveis plasmáticos de omentina e NO em 25 indivíduos com sobrepeso e obesidade. O grupo controle foi composto por 28 participantes sedentários que não eram obesos nem com sobrepeso. A reatividade microvascular foi obtida pela medida do fluxo sanguíneo da pele do dedo anelar da mão direita com LDF, que é um método não invasivo de avaliação.



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Com este método, objetivou-se examinar a resposta da hiperemia reativa pós-oclusiva dos pacientes. Os participantes de ambos os grupos nunca seguiram um cronograma regular de exercícios em sua vida.

Resultados: com o exercício regular houve diminuição estatisticamente significativa dos níveis de glicose ($p=0,008$), de colesterol ($p=0,05$) e de triglicerídeos ($p=0,048$), enquanto o índice de massa corporal e os níveis de lipoproteínas de alta e baixa densidade não se alteraram significativamente no grupo com sobrepeso/obesidade. Além disso, o nível de omentina aumentou significativamente ($p=0,01$), mas o nível de NO não apresentou modificações significativas. Observou-se, também, que as modificações nos níveis de omentina e NO mensurados antes e após o exercício físico foram significativamente correlacionados ($r=0,57$). Em relação à microcirculação, os valores do fluxo de repouso ($p=0,001$) e do valor de fluxo de pico e da LDF ($p=0,001$) aumentaram após o exercício físico.

Conclusão: nosso estudo mostra que o exercício físico moderado afeta a reatividade microvascular e os níveis plasmáticos de omentina em indivíduos com sobrepeso e obesidade

Palavras-chave: fluxometria laser doppler, óxido nítrico, omentina, obesidade, exercício físico.

Introduction

Cardiovascular diseases are significant reasons of morbidity and mortality in obese individuals. Endothelial dysfunction and atherosclerosis are highly likely severe consequences of obesity induced cardiovascular diseases (1). In obesity, increased free fatty acids can cause mitochondrial dysfunction and free oxygen radical formation and eventually endothelial dysfunction. As a result of increased free fatty acids and accompanying activated inflammatory pathways, insulin resistance and oxidative stress may be generated. Depending on this, bioavailability of endothelium-derived nitric oxide (NO) reduces and by this way NO-dependent vascular dilatation may deteriorate (2). Moreover, obesity leads to malfunction in particularly visceral type of adipose tissue. Adipose tissue has been widely considered as an endocrine tissue for recent decades. It releases several kinds of polypeptides which are collectively called as "adipokines". As a result of cytokines originating from adipose tissue omentin levels decrease in obesity. That decrease usually causes endothelial dysfunction by several ways (by decreasing eNOS phosphorylation, decreasing insulin sensitivity, or stimulating several vasoconstrictor mechanisms) (3, 4). Endothelial

dysfunction is regarded as the first ascertained deterioration in pathophysiological course of cardiovascular diseases.

It was shown that cardiovascular risk factors calm down and omentin level increases with exercise in obese subjects. Increase in physical activity and changes in lifestyle have positive effects on endothelial function and microvascular reactivity in obese subjects (3, 5). Effects of exercise may be related with increased NO release due to shear stress, increased eNOS synthase, attenuation of inhibitory effects of oxyradicals, which are certain radicals involving reactive oxygen atoms and emerging from endogenous cellular functioning, on NO orchestrated pathways (6, 7).

Laser-Doppler flowmetry (LDF) portrays both qualitative and quantitative variables regarding territorial blood flow supplementation and information acquired by LDF could not be readily reached by any other methods. The technique is based on quantifying the Doppler shift stimulated by erythrocytes in motion towards the light shed upon. Microvascular circulation and supplementation are delicately regulated by tissue requirements. So, the more effective regulation, the healthier and more compliant microvascular network you have. Inevitably, each pathological condition leading cardiovascular diseases poses an undeniable potential to deteriorate microvascular circulation. Then, a better understanding of microvascular changes during the course of cardiovascular diseases also provides a clearer insight into the pathology itself. Besides, consequences of therapeutic interventions could be plainly and much more precisely revealed by handling microvascular improvement.

This study aims to investigate the changes in plasma NO and omentin levels that are believed to mitigate cardiovascular risk factors and promote microcirculation and skin blood flow following regular physical exercise in overweight or obese individuals.

Material and method

In this research, male and female subjects who were diagnosed as obese or overweight,

between the ages of 33–65, already enrolled to Healthy Living and Obesity Centre of Gaziantep Province Municipality and never participated in any regular exercise schedule, were conducted to the study based on voluntariness of the individual. The subjects in the control group were also included on voluntary basis and they were neither obese nor overweight and have never attended to any exercise schedule before, as well. Each participant was informed about the study and an informed consent form was obtained from each and the study was conducted in accordance with the principles set forth by Helsinki Declaration. Ethics committee approval was obtained for the study with project number 337, dated 10.11.2014.

Twenty-five male and female volunteer participants ($n=25$), who are diagnosed as overweight or obese and have never been attended to a regular exercise schedule, had a mean age of 48 ± 9.7 . Twenty-eight normal weight subjects ($n=28$), who also had adopted a sedentary life and never participated in any regular exercise schedule, had a mean age of 43 ± 8.4 , were in the control group. The age, gender, height, weight, and body mass index (BMI) of all participants were recorded. Total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), fasting blood glucose levels were detected in the blood samples of all volunteers, taken after 12-hour fasting. For detection of omentin (Eastbiopharm CK-E11629, China) and NO (Cayman Catalog No: 780001) levels in blood samples, commercial ELISA kits were used.

After taking blood samples from volunteer subjects who were diagnosed as obese or overweight and who had never followed up a regular physical exercise schedule, they were undertaken through a 12-week, five days per week exercise schedule, each session of which was composing of 60-minute walking and low tempo jogging. For the control group no physical exercise program was applied. Initial measurements of the subjects were taken one week before beginning exercise schedule and last measurements were taken one week after having the schedule finished. The subjects, in both control and exercise groups,

also undertook a diet program. The diet program applied to each subject was a Mediterranean type of diet program. Neither calorie restriction nor complete removal of any nutrients from the diet was postulated. Instead, the diet program was principally constituted in a way that suggests moderate amounts of poultry, and fish along with very low amounts of red meat as protein sources, and plenty amount of green vegetables, abundance of olive oil, daily fresh fruit, and red wine. Dietary receipts were displaying slight differences according to the habitudes and cultural features of the subjects, but all were in the frame of Mediterranean type of diet, consistent with the European Society of Cardiology recommendations.

Evaluation of the microcirculation

Upper extremity skin blood flow rate was measured by a non-invasive LDF (Periflux System 5000, Perimed, Sweden). After 12-hour fasting the subjects were rested in supine position for 10 minutes in a quiet place with a room temperature of 20–25 °C. Then, a cuff suitable for proximal phalanx of ring finger of the right hand was placed. The probe of LDF was attached to the distal phalanx of the same finger. Initially, the basal skin blood flow rate was measured for 3 minutes. Then, the cuff was inflated to 250 mmHg for arterial occlusion and the cuff was deflated after 3 minutes in which period skin blood flow was recorded continuously. Afterwards, the measurement went on for 3 minutes more (**Figure 1**). Post occlusive reactive hyperaemia response, with a sudden peak and steadily decreasing integrity, was assessed. The measurements were expressed as random perfusion unit (PU). For the blood flow rate measurement during resting period rest flow (RF) and for the peak blood flow rate measurement after occlusion peak flow (PF) values were recorded (8).

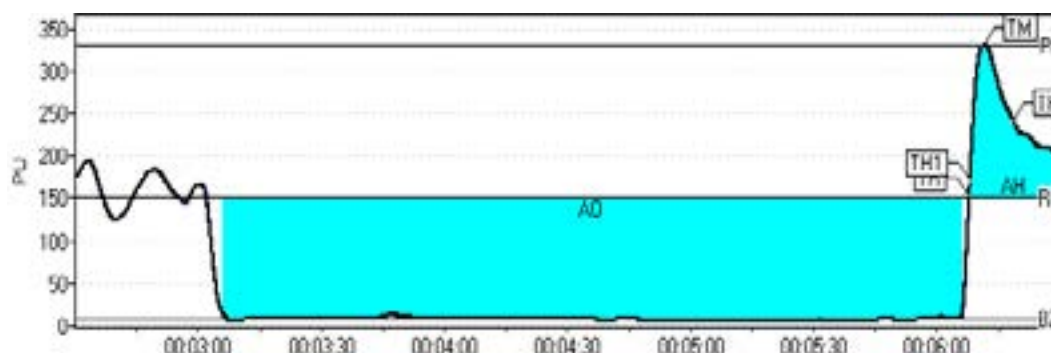


Figure 1. Post occlusive hyperaemia of a subject in obese/overweight group before starting exercise schedule, illustrated in the figure; RF and PF were detected as 151.13 and 330.71, respectively. On contrary to that, RF and PF of the same subject were detected as 375.68 and 557.39, respectively, after completing the exercise schedule (not illustrated) ($p=0.001$ and $p=0.002$). AH; arterial hyperaemia, AO; arterial occlusion, PF; peak flow, PU; perfusion unit, RF; rest flow, TH1; time to half before hyperaemia, the time it takes after the release of the occlusion for perfusion to reach the midpoint between no flow and peak flow, TH2; half time of hyperaemia, the time it takes after the release of the occlusion, post-hyperaemia, for perfusion to reach the midpoint between peak flow and baseline, TM; time to peak flow, TR; time to recovery.

Statistical method

The Kolmogorov–Smirnov test was used for detecting whether the data ranks in a normal distribution or not. The Mann–Whitney U and Wilcoxon tests were used to compare non-normally distributed variables in two independent groups and two dependent groups, respectively. Spearman's rank correlation coefficient was used in order to test existence of any relation among quantitative variables. For descriptive statistics of continuous variables mean±standard deviation; for descriptive statistics of categorical variables frequencies and percentages values were presented. For statistical analysis, SPSS for Windows version 22.0 package program was used and $p<0.05$ was assumed as statistically significant.

Results

When the control group was compared to the overweight/obese group not undergone the appointed exercise schedule yet, weight ($p<0.001$), BMI ($p<0.001$), glucose ($p<0.001$), TC ($p<0.001$), TG ($p<0.009$) and HDL ($p<0.03$) were found to be significantly different. However, no difference was observed between LDL levels. When the control group was compared to the

overweight/obese group fulfilled the appointed exercise schedule, weight ($p<0.001$), BMI ($p<0.001$), TC ($p<0.03$), and HDL ($p<0.001$) were found to be significantly different from each other. Notwithstanding, glucose, TG and LDL levels did not differ (**Table 1**). It was shown in table 1 that there was a statistically significant difference in glucose ($p=0.008$), TC ($p=0.05$) and TG ($p=0.048$) levels between overweight/obese group not started exercise schedule yet and overweight/obese group fulfilled 12-week exercise program. Nevertheless, no significant difference was found among weight, BMI, HDL, and LDL.

As for the **Table 2**, when overweight/obese group before starting exercise schedule and the control group were compared there was a statistically significant difference between omentin ($p=0.001$) and NO ($p=0.005$) levels. Before applying exercise program, NO and omentin levels were truthfully lower in overweight/obese group. When post-exercise overweight/obese group and the control were compared no statistically significant difference was found. Then, when pre-exercise and post-exercise values of overweight/obese group were compared, the increase in the omentin levels was significant ($p<0.01$). Despite the fact NO

level of the post-exercise group was not detected to have meaningfully increased in comparison to pre-exercise value, increment amount provided a new level which also did not differ statistically from the control group, whereas pre-exercise value did already differ. Moreover, according to Spearman's rank correlation, a significant mild correlation was observed between the amount of increase in omentin, and NO levels measured before starting and after fulfilling the exercise schedule in the overweight/obese group ($r=0.57$).

As we hope, there was a statistically significant difference between RF ($p=0.001$) and PF ($p=0.002$) measurements of the overweight/obese group before starting exercise schedule and the control group, the measurements were lower in the overweight/obese group before starting exercise accordingly (**Figure 1**). However, those measurements did not differ from each other when the control group and the overweight/obese group fulfilled the 12-week exercise schedule were compared (**Table 2**).

TABLE 1 – Demographic features of the groups and biochemical values.

	Control group (n=28)	Exercise group, before starting exercise schedule (n=25)	Exercise group, after completing exercise schedule (n=25)
Age, years	43.1±8.4	48.2± 9.7	48.2±9.7
Weight, kg	67.7±13.3 ^{†‡}	88.2±13.4 [*]	84.6±13.1 [*]
Body mass index, kg /m ²	23.2±3.2 ^{†‡}	33.1±4.6 [*]	32.0±4.8 [*]
Total cholesterol, mmol/L	179.6±49.4 ^{†‡}	239.0±39.8 ^{*,†}	220.5±43.9 ^{*,†}
Triglycerides, mmol/L	110.3±73.1 [†]	305.0±171.4 ^{*,†}	178.9±110.5 [†]
Glucose, mg/dL	75.1±8.7 [†]	97.1±15.2 ^{*,†}	86.8±13.2 [†]
LDL, mg/dL	122.0±51.5	151.0±40.2	137.2±37.8
HDL, mg/dL	51.8±15.4 ^{†‡}	58.2±15.1 [*]	62.3±16.7 [*]

HDL, high-density lipoprotein; LDL, low-density lipoprotein. The Mann-Whitney U test was used for both control – pre-exercise and control – post-exercise group comparisons. The Wilcoxon test was used for comparison of pre-exercise and groups. *When compared to control group ($p<0.05$). † When compared to pre-exercise group ($p<0.05$). ‡ When compared to post-exercise group ($p<0.05$).

TABLE 2 – Laser-Doppler flowmetry results and omentin and NO levels of groups prior to the exercise and after the exercise.

	Control group (n=28)	Exercise group, before starting exercise schedule (n=25)	Exercise group, after completing exercise schedule) (n=25)
Omentin, ng/dl	491.5±188.1 [†]	323.8±256.5 ^{*,†}	502.7±253.4 [†]
NO, µmol/L	135.5±57.4 [†]	102.4±68.6 [*]	123.1±60.2
RF, PU	350.0±120.3 [†]	218.3±127.9 ^{*,†}	384.8±117.2 [†]
PF, PU	514.5±163.7 [†]	367.3±132.3 ^{*,†}	583.1±110.4 [†]

NO, Nitric oxide; PF, Rest flow; PU, random perfusion unit; RF, Rest flow. The Mann-Whitney U test was used for both control – pre-exercise and control – post-exercise group comparisons. The Wilcoxon test was used for comparison of pre-exercise and groups. *When compared to control group ($p<0.05$). † When compared to pre-exercise group ($p<0.05$). ‡ When compared to post-exercise group ($p<0.05$).

Discussion

The endothelial dysfunction underlies the cardiovascular diseases and has influence on prognosis. Endothelial dysfunction occurs when vasoconstriction–vasodilation balance of endothelia begins to turn in favour of vasoconstriction. It is believed that obesity caused pathologies like hypertension, dyslipidaemia, hyperglycaemia, insulin resistance, chronic inflammation, and atherosclerosis play certain roles in the formation of endothelial dysfunction (9, 10).

It is thought that endothelial damage that initiates the cardiovascular diseases, starts from the microvascular area and LDF technique can be used for evaluating the microcirculation (11). The method to be used to detect endothelial dysfunction had better be reliable, non-invasive, easily accessible, and able to evaluate response to treatment. Because there is no such test in practice, the endothelium–dependent vasoactivity and endothelial functions are being assessed by concentrating on the markers in blood circulation. LDF technique is considered substantial especially for the monitoring of skin microcirculation. Accordingly, since the endothelial dysfunction causes systemic manifestations eventually, evaluation of peripheral vessels with non-invasive LDF method would provide a veracious prediction about future of individual. LDF examination of the skin microcirculation is only a surrogate for detecting microvascular injury and may show temporary spontaneous variations. However, studies have shown that impairment of skin microcirculation is directly related to microcirculatory deteriorations in coronary, renal, and muscle. Then, it might be a reliable ancestor marker of all cardiovascular complications. For evaluation, different provocation tests can be used in LDF technique (thermal stimulus, iontophoresis, post-occlusive reactive hyperemia) but it was shown in certain studies that results are similar (12, 13). Additionally, impairment of skin microcirculation, which can be detected non-invasively beforehand, may be a harbinger of a serious vasculopathy that may progress primarily to kidney or heart diseases (13). It has been

demonstrated by acetylcholine coronary artery infusion and brachial flow–mediated dilation tests that patients with coronary artery dysfunction also exhibit a pithy attenuated vasodilation response of brachial artery, suggesting non-invasively evaluation of skin blood flow as cardiovascular disease marker (14). It has also been revealed that the measurements of the LDF technique are reliably reproducible. In a study conducted with healthy non-smoker and male subjects, it was stated that peak reactive hyperaemia values did not show a statistically significant difference in measurements made from different parts of the forearm or from the same region at two–day interval (15). In hypertensive patients, skin blood flow rate measured with LDF and muscle blood flow rate (strain gauge venous plethysmography) results showed parallelism with each other (16). In the study carried out with the coronary artery patients and healthy controls, the post occlusive reactive hyperaemia and microcirculation response were evaluated, and it was found that in coronary artery patients the vasodilation response was detected to be decreased. Since it is not invasive, simple to use and can be repeatable, it is thought that LDF also could be used in the patients' diagnosis and follow up (17). In obese subjects it was shown with LDF that acetylcholine–induced endothelium dependent vasodilation response was found to be decreased (18). On contrary to that, in both aerobic or anaerobic exercising athletes, it was observed to be increased (19,20). In hypertensive overweight subjects the physical exercise increased the endothelium–dependent vasodilation by increasing the post ischemic peak value that was measured with LDF (21). In our study, in obese subjects, RF and PF rates measured with LDF were specified to be increased after physical exercise of which reason is thought hypothetically to be an increase in endothelium–dependent vasodilation. In a similar study, it was shown that in overweight and obese subjects the forearm blood flow response to acetylcholine increased after physical exercise. However, there was no change in BMI, similar to our study (22).

Obesity decreases NO bioavailability and thus

it was thought that the vascular endothelia loses its anti-atherogenic feature and NO dependent dilation deteriorates (2). Regular physical exercise probably increases NO bioavailability depending upon the increase in endothelial NO synthase (eNOS) and antioxidant defence capacity (16,23). In overweight children, active dance exercise for 12 weeks caused an increase in flow mediated dilation without changing the NO production (24). Similarly, the NO levels overweight/obese subjects did not increase significantly related to the physical exercise in our study but in LDF, the vasodilation enhanced.

Omentin is an adipocytokine secreted by adipose tissue and it is thought that, its lower levels than normal might be an indicator for cardiovascular diseases. It was shown that the plasma concentration of omentin and gene expressions in visceral adipose tissue decrease in obesity. The oxidative stress and pro-inflammatory cytokines may decrease omentin and may cause endothelial dysfunction in obesity (25). It was stated that omentin levels are inversely proportional with BMI, leptin, insulin resistance and waist circumference; and directly proportional with HDL and adiponectin (3,4). In our study, the blood omentin levels in obese subjects before exercise were lower than the subjects' levels in control group. At the same time, glucose, TC, and TG levels decrease statistically significantly after physical exercise in comparison to pre-exercise values. Besides, it was thought that the effects of omentin on endothelia may be as a consequence of its role in preventing factors like ICAM-1, NF- κ B and VCAM-1 (26). In vitro studies show that it increases NO synthase. Moreover, it is thought that omentin has an effect on the activation of AMPK/eNOS/NO paths and probably has an anti-inflammatory effect on vascular endothelial cells (7). All of these results prompt to think that omentin prevents endothelial dysfunction with different paths, and enhanced vascular dilatation seems to be the preeminent outcome of an increase in omentin level. In our study, it was shown that the more increased omentin levels are encountered the more boosted vasodilation in microcirculation is observed.

It was shown that although there was no change in weight, the omentin levels increased by 10% in obese women after the physical exercise (27). In a similar study, the omentin levels increased after 12-week physical exercise schedule composing of one hour of exercise three days a week however, it was thought that a more forcefully exercise period could have been more effective (28). Previous to that, Wangs declared that a midlevel intensity exercise program resulted in enhanced endothelial dependent vasodilation, but vasodilation ability of endothelia returned to former level when the exercise program was not kept going anymore (29). These results make us think that intensity and regularity of exercise schedule which should be designed in regard of health characteristics of an individual determine how much benefit would be gained. After all, 12-week physical exercise in our study raised omentin level in overweight and obese subjects. As mentioned, omentin has reasonably regulatory effect over eNOS, and also exercise can directly increase NO level by exacerbating the vascular shear stress and building blood flow rate up (30). Moreover, physical exercise may show its relaxing effect on dermal microcirculation by increasing NO's biological availability or increasing NO's vascular smooth muscle sensitivity (31). In our results, it was observed that increase in omentin levels correlated with NO increase. Since we did not find the increase in NO levels to be statistically significant, we think that the vasodilator activity of omentin due to physical exercise is not only related to the increase in NO, but also that there is a possible inhibitory effect of omentin on vasoconstrictor mechanisms.

In conclusion, our study showed that medium level physical exercise have significant effects on microvascular reactivity and omentin plasma levels in overweight and obese subjects. This data supports the importance of aiming a lifestyle change as a therapeutic approach at first stage in order to heal microvascular endothelial dysfunction in obese patients. However, the fact that different or conflicting results have been revealed in similar studies suggests that personalizing

the exercise programs of obese individuals by relevant experts may be a more effective way to reverse microvascular or endothelial damage. The measurement of reactive hyperaemia in skin with LDF is a simple and non-invasive method for measuring the microvascular function in obese patients. LDF is seen as a promising method for showing the effects of drug free treatment in obese patients. Moreover, the plasma omentin concentration can be a useful indicator for evaluating endothelial function.

Notes

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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