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Impact of a ketogenic diet on intestinal microbiota, cardiometabolic, and glycemic control parameters in patients with Type 2 diabetes mellitus.

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Keywords: ketogenic diet; Type 2 diabetes mellitus; intestinal flora; glucagon like peptide-1; glycosylated hemoglobin.

Abstract. A ketogenic diet (KD), characterized by high fat and low carbohydrate intake, has been proposed as a therapeutic option for Type 2 Diabetes Mellitus (T2DM). One hundred individuals with T2DM were selected and divided into a control group (CG) and an observation (OG) group, with 50 patients in each group, to investigate the effects of a KD on the intestinal flora, Glucagon Like Peptide-1 (GLP-1), and HbA1c levels in T2DM patients. Individuals in the CG were given standard treatment and diet, while patients in the OG were given a KD based on the CG. The blood glucose index, blood lipid index, HbA1c, GLP-1 levels, physical examination, and intestinal flora were compared in both groups. The FPG, HbA1c, two h PG, HOMA-IR TG, TC, and LDL-C levels in the two groups were reduced when compared to those before treatment ($p<0.05$), and the decreases in the OG were more significant than in the CG ($p<0.05$), while the levels of GLP-1 in the two groups were increased compared to those before treatment, those in the OG were significantly increased when compared to the CG ($p<0.05$). After treatment, waist circumference, BMI, body mass, and the levels of *Enterococcus faecalis (E. faecalis)* and *Escherichia coli (E. coli)* of the two groups were reduced compared to indicators before treatment ($p<0.05$), and those in the OG were even lower than those in the CG ($p<0.05$). In conclusion, these findings underscore the KD's potential to act as an efficacious dietary strategy in managing T2DM.

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Impacto de una dieta cetogénica en la microbiota intestinal y los parámetros de control cardiometabólico y glucémico en pacientes con diabetes mellitus tipo 2.

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Palabras clave: dieta cetogénica; diabetes mellitus tipo 2; flora intestinal; péptido-1 similar al glucagón; hemoglobina glicosilada.

Resumen. Una dieta cetogénica (KD), caracterizada por una ingesta alta en grasas y baja en carbohidratos, se ha propuesto como una opción terapéutica para la diabetes mellitus tipo 2 (DM2). Se seleccionaron cien individuos con DM2 y se dividieron en un grupo control (GC) y un grupo de observación (GO), con 50 pacientes en cada grupo, para investigar los efectos de una dieta cetogénica sobre los niveles de la flora intestinal, el péptido similar al glucagón-1 (GLP-1) y la HbA1c en pacientes con DM2. Los individuos del GC recibieron tratamiento y dieta estándar, mientras que los pacientes del GO recibieron el tratamiento estándar similar al GC, más una dieta cetogénica. En ambos grupos se compararon el índice de glicemia, el índice de lípidos en sangre, la HbA1c, los niveles del GLP-1, el examen físico y la flora intestinal. Los niveles de FPG, HbA1c, 2h PG, HOMA-IR TG, TC y LDL-C en los dos grupos se redujeron en comparación con los de antes del tratamiento ($p<0,05$), y las disminuciones en el GO fueron más significativas que en el grupo GC ($p<0,05$), mientras que los niveles de GLP-1 en los dos grupos aumentaron en comparación con los de antes del tratamiento, los del GO aumentaron significativamente en comparación con el GC ($p<0,05$). Después del tratamiento, la circunferencia de la cintura, el IMC, la masa corporal y los niveles de *Enterococcus faecalis (E. faecalis) y Escherichia coli (E. coli)* de los dos grupos se redujeron en comparación con los indicadores antes del tratamiento ($p<0,05$), y los del GO fueron incluso más bajos que los del GC. ($p<0,05$). En conclusión, estos hallazgos subrayan el potencial de la KD para actuar como una estrategia dietética eficaz en el tratamiento de la DM2.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder marked by elevated blood sugar levels [1]. T2DM is linked to metabolic syndrome and insulin resistance. It is influenced by genetics, obesity, inactivity, and ethnicity [2, 3]. The prevalence of T2DM varies globally, with a higher incidence in developed countries. As per the most recent report from the International Diabetes Federation (IDF), the worldwide incidence of T2DM among adults stood at 536.6 million individuals (10.5%) in 2021. It is projected that the number of individuals living with diabetes will reach 783.2 million people (12.2%) globally by the year 2045 [4].

From a pathophysiological perspective, T2DM is associated with insulin resistance, wherein the body's cells are less responsive to insulin, and a gradual failure of pancreatic β-cells to compensate for this increased

demand [5]. This dysfunction is reflected in the hallmark signs and symptoms of T2DM, which include polyuria, polydipsia, polyphagia, and weight loss [6].

Long-term complications of T2DM are broad-ranging and include microvascular damage leading to retinopathy, neuropathy, and nephropathy, as well as macrovascular complications such as coronary artery disease, peripheral arterial disease, and cerebrovascular disease [7, 8].

Diagnosis of T2DM is typically confirmed through several tests, including fasting plasma glucose (FPG), 2-hour plasma glucose (2-h PG) during an oral glucose tolerance test (OGTT), and hemoglobin A1c (HbA1c) levels, which reflect the mean blood glucose levels over the previous two to three months [9].

Treatment modalities for T2DM include lifestyle interventions, oral hypoglycemic agents, non-insulin injectables, and insulin therapy [10, 11]. Among the dietary strategies, the KD (a high-fat, adequate-protein, low-carbohydrate diet) has emerged as a potential therapeutic option [12, 13]. This diet aims to induce a state of ketosis, where the body utilizes fat as a primary energy source instead of glucose [14].

The KD has been associated with alterations in the gut microbiota, which play a crucial role in metabolic health [15]. A shift in intestinal flora could potentially influence the incretin hormone glucagon-like peptide-1 (GLP-1), which promotes insulin secretion and improves glycemic control. Furthermore, the KD could influence HbA1c levels, providing a broader metabolic benefit for patients with T2DM [16,17].

However, the literature presents a paucity of comprehensive studies that holistically examine the effects of a KD on both the intestinal microbiota and the serum levels of GLP-1 and HbA1c in patients with T2DM. Therefore, this study aims to explore the effects of a KD on intestinal flora and serum GLP-1 and glycosylated hemoglobin levels in T2DM patients.

PATIENTS AND METHODS

This study was conducted as an interventional study with a randomized controlled trial (RCT) design. The study spanned over six months, from June 2021 to June 2022, at the South of Guang'anmen Hospital.

Based on the random number table method, 100 T2DM patients were selected and divided into a control group (CG) and an observation group (OG), with 50 patients in each group. As shown in Table 1, there were no significant differences between the two groups in general data ($P>0.05$).

Our hospital's Ethics Committee reviewed and approved the study, and patients signed the informed consent form.

Inclusion criteria: ① Patients with T2DM were initially diagnosed through clinical signs and symptoms (polyuria, polydipsia, polyphagia, unexplained weight loss, fatigue,

Table 1
Clinical data of patients.

Group	n	Sex(n)		Age $\bar{x} \pm SD$	BMI (kg/m^2) $\bar{x} \pm SD$
		Male	Female		
CG	50	31	19	53.11±9.69	27.32±5.23
OG	50	32	18	52.64±10.53	27.06±5.56
t/χ^2		0.043		0.232	0.241
p		0.836		0.817	0.810

CG: Control group, OG: Observation group, $\bar{x} \pm SD$: mean ± standard deviation (SD), BMI: Body mass index, t: t-test, χ^2: chi-square test.

and blurred vision), and serological indicators (FPG >7.0 mmol/L or 126 mg/dL; a plasma glucose concentration equal to or exceeding ≥11.1 mmol/L or 200 mg/dL two hours after a 75-g oral glucose tolerance test (OGTT); HbA1c >6.5% or higher was also indicative of T2DM) [18, 19], ② Patients with good treatment compliance; ③Complete and accurate medical records.

Exclusion criteria: ① Patients with other serious diabetic complications such as ketoacidosis; ② Patients with other endocrine diseases; ③ Heart, liver, and kidney failure patients; ④ Patients with drug allergy episodes in the past.

The patients in the CG were given standard treatment: patients were instructed to control their diet, exercise appropriately, quit smoking, and limit alcohol consumption, and blood glucose was closely monitored. Patients in the OG were given a KD based on treatment in the CG. High-protein and low-carbohydrate KD treatment included 1/5-2/5 of fat, 2/5 of protein, 1/5 of carbohydrate, keeping regular three meals. This diet limits carbohydrate intake to around 20-50 grams daily and increases fats such as meat, fish, eggs, nuts, and healthy oils. On the other hand, adjusting protein consumption is also part of this diet; if much protein is consumed, it can be converted to glucose and may slow the transition to ketosis. The intake of fat was rich in ω-3 mainly, such as sardines, salmon, tuna, and other sources of this fat. The amount of drinking water was more than 2000 mL/d, multiple mineral vitamins needed to be supplemented, and the amount of exercise remained at the previous level. Both groups of patients were treated continuously for six months.

Serological indicators

The two groups of patients had 5 mL of fasting peripheral venous blood collected in the morning before and after treatment, centrifuged at 3000 r/min, and the supernatant stored at 4°C. A radioimmunoassay was used to measure fasting blood glucose (FPG) and postprandial blood glucose (2h PG), ELISA was used to detect fasting insulin (FINS), and an insulin resistance index was used to determine insulin resistance (HOMA-IR=(FPG×FINS)/22.5. All the kits were provided by the Shanghai Enzyme Linked Biotechnology Co., Ltd. and operated strictly according to the specifications of the kit instructions. The levels of triglycerides (TG) and total cholesterol (TC) were detected by ELISA, and the levels of low-density lipoprotein cholesterol (LDL-C) were detected by the surfactant clearance method. ELISA detected serum HbA1c and GLP-1 levels.

Physical examination indicators

Intestinal flora

Before and after treatment, 0.1g of fresh feces from the two groups of patients were collected, mixed with normal saline, and inoculated into the culture medium containing aerobic and anaerobic bacteria, respectively. The aerobic bacteria mainly refer to *bifidobacteria* and *lactobacillus*. The culture environment was aerobic; the temperature was set at 37°C, and the time was 48h. Anaerobic bacteria refer to *E. faecalis* and *E. coli*. The air extraction and ventilation method was adopted, and the incubation time was 72h. After the culture, the *BIOLOG* automatic microbial identification system detected the *Bifidobacterium, Lactobacillus, Fecal Enterococcus, and E. coli* levels.

Statistical methods

IBM SPSS 20.0® was used for statistical analysis, and the counting data were χ^2. The measurement data were expressed by mean ± standard deviation (Mean±SD) and compared by the t-test. The difference was statistically significant when $p<0.05$

RESULTS

Blood glucose indicators in each group

There was no difference ($p>0.05$) in blood glucose between the two groups before treatment. After treatment, the levels

of FPG, 2h PG, and HOMA-IR in both groups were reduced compared to those before treatment ($p<0.05$), and those in the OG were even more reduced than those in the CG ($p<0.05$), as shown in Table 2.

Blood lipid indexes in each group

Blood lipid indexes between the two groups were no different before treatment ($p>0.05$). After treatment, the levels of TG, TC, and LDL-C in the two groups were reduced compared to those before treatment ($p<0.05$), and the levels in the OG were even more reduced than those in the CG ($p<0.05$) (Table 3).

HbA1c and GLP-1 levels in each group

Before treatment, HbA1c and GLP-1 levels between the two groups were no different ($p>0.05$); after treatment, those in the two groups were raised compared to those before treatment, and the levels of HbA1c in the CG were higher than those in the OG ($p<0.05$). The concentration of GLP-1 in the OG was higher than in the CG after six months of treatment ($p<0.05$), as shown in Table 4.

Physical examination indexes in each group

Before treatment, the two groups' waist circumference, BMI, and body mass were no different ($p>0.05$). After treatment, waist circumference, BMI, and body mass of the two groups were reduced compared to those before treatment, and the indicators of the OG were even more reduced than in the CG ($p<0.05$) (Table 5).

Comparison of intestinal flora in each group

Before treatment, the intestinal flora between the two groups was no different

Table 2
Blood glucose indicators in each group before and after six months of treatment.

Group	N	FPG (mmol/L)		2h PG (mmol/L)		HOMA-IR	
		Before	After	Before	After	Before	After
CG	50	8.45±1.24	7.29±0.98*	13.01±1.72	10.22±1.47*	3.86±0.72	2.87±0.55*
OG	50	8.32±1.07	6.57±1.01*	12.83±1.66	8.63±1.25*	3.77±0.67	2.43±0.48*
t		0.561	3.618	0.533	5.827	0.647	4.262
p		0.576	0.000	0.596	0.000	0.519	0.000

CG: Control group, OG: Observation Group, FPG: Fasting Plasma Glucose, 2h PG: 2-hour Postprandial Glucose, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, t: t-test, values are expressed as Mean±SD *: $p<0.05$ compared with the patients in this group before treatment.

Table 3
Blood lipid indexes in each group before and after six months of treatment.

Group	N	TG		TC		LDL-C	
		Before	After	Before	Before	Before	After
CG	50	2.57±0.61	1.97±0.42*	5.23±0.96	4.41±0.91	3.69±1.02	3.01±0.76*
OG	50	2.53±0.57	1.62±0.38*	5.21±1.13	3.94±0.77	3.63±0.95	2.65±0.41*
t		0.339	4.370	0.095	2.788	0.304	2.948
p		0.736	0.000	0.924	0.006	0.762	0.004

CG: Control group, OG: Observation group, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol. Values are expressed as mmol/L. t: t-test, *: $p<0.05$ compared with the patients in this group before treatment, * $p<0.05$.

Table 4
HbA1c and GLP-1 levels in each group before and after six months of treatment.

Group	N	HbA1c (%)		GLP-1 (μ mol/L)	
		Before	After	Before	After
CG	50	8.41±1.12	7.51±1.09*	6.72±0.88	11.34±1.11*
OG	50	8.53±1.18	6.64±0.87*	6.64±0.52	14.43±2.28*
t		0.522	-4.411	-0.553	8.616
p		0.603	0.000	0.581	0.000

CG: Control group, OG: Observation group, HbA1c: hemoglobin A1c, GLP-1: glucagon-like peptide 1, t: t-test, * p<0.05 compared with the patients in this group before treatment.

Table 5
Physical examination indexes in each group before and after six months of treatment.

Group	N	Weight (kg)		BMI (kg/m^2)		Waist circumference (cm)	
		Before	After	Before	After	Before	After
CG	50	90.02±10.80	72.14±9.63*	30.58±2.81	25.70±1.42*	98.63±3.41	86.84±3.25*
OG	50	89.12±10.72	67.76±9.58*	30.46±2.92	24.25±1.35*	98.56±3.35	80.62±2.20*
t		-0.418	-2.280	-0.209	-5.233	-0.104	-11.207
p		0.677	0.025	0.835	0.000	0.918	0.000

CG: Control group, OG: Observation group, BMI: body mass index, t: t-test, *: p<0.05 compared with the patients in this group before treatment.

Table 6
Intestinal flora in each group before and after six months of treatment.

Group	N	*Bifidobacterium*		*Lactobacillus*		*E. faecalis*		*E. coli*	
		Before	After	Before	After	Before	After	Before	After
CG	50	7.54±0.95	8.15±0.86*	6.93±0.99	7.58±0.82*	8.22±0.83	7.42±0.72*	9.46±1.15	8.16±1.18*
OG	50	7.62±1.14	8.82±0.76*	6.84±0.92	8.12±0.93*	8.16±0.76	6.56±0.77*	9.64±1.23	7.24±0.87*
t		0.381	4.128	-0.471	3.080	-0.377	-5.769	0.756	-4.437
p		0.704	0.000	0.639	0.003	0.707	0.000	0.452	0.000

CG: Control group, OG: Observation group. Values are expressed as lgCFU/g, t: t-test, *: p<0.05 compared with the patients in this group before treatment.

(p>0.05). After treatment, the levels of *Bifidobacterium* and *Lactobacillus* in the two groups were increased compared to those before treatment, and those in the OG were higher than in the CG (p<0.05). After treatment, the levels of *E. faecalis* and *E. coli* in the two groups were reduced to those before treatment (P<0.05), and the levels in the OG were even lower than those in the CG (p<0.05) (Table 6).

DISCUSSION

The ketogenic diet (KD) has been increasingly studied for its potential therapeutic effects in various health conditions, including type 2 diabetes mellitus (T2DM) [20]. T2DM is a chronic condition characterized by insulin resistance and impaired glucose metabolism [21]. This study aimed to investigate the impact of a KD on the intestinal

microbiota and the serum levels of glucagon-like peptide-1 (GLP-1) and glycosylated hemoglobin (HbA1c) in patients with T2DM.

The present study's findings suggest that patients with T2DM who followed a KD for six months exhibited significant improvements in their serum levels of GLP-1 and HbA1c, as well as their blood glucose and lipid profiles, compared to the control group receiving standard treatment. Additionally, there were notable changes in the composition of the intestinal microbiota, with an increase in beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, and a decrease in potentially harmful bacteria like *E. faecalis and E. coli*.

Several studies have investigated the impact of a KD on weight, blood glucose levels, and lipid profiles in patients with T2DM. In line with the present study, the research findings suggest that a KD can induce positive changes in these parameters, offering potential benefits for managing T2DM. Li *et al.*'s study results show that following a KD can lead to a decrease in fasting blood glucose and glycosylated hemoglobin levels in T2DM patients, which indicates an improvement in blood glucose management [22]. Zhou *et al.*[23] also conducted a meta-analysis to investigate the role of KD in controlling body weight and managing blood sugar in overweight patients with T2DM. The results show that the KD significantly reduces body weight, reduces waist circumference, reduces glycosylated hemoglobin and triglycerides, and increases high-density lipoproteins (HDL)[23].

Additionally, the improvement in lipid profiles, particularly the reduction in triglyceride levels, is corroborated by Yuan *et al.* [24]. The KD's impact on lipid profiles, especially triglyceride levels, is likely due to its effects on insulin secretion and lipid metabolism. By reducing carbohydrate intake and increasing fat intake, the diet leads to a decrease in insulin secretion, which in turn reduces the conversion of excess carbohydrates into triglycerides in the liver [25]. Additionally, the diet's high-fat content provides a source of energy that is less likely to be stored as triglycerides in adipose tissue, further contributing to the reduction in triglyceride levels [26].

The efficacy of insulin action is ensured through a cellular signalling cascade, which encompasses membrane insulin receptors (IRS) and intracellular proteins (PI3K and AKT). Critical for the uptake of plasma glucose into tissues, these interactions between proteins play a vital role. Conversely, deficiencies in cellular signal transduction and insulin responses to insulin stimulation (IR) can disrupt glucose regulation, consequently contributing to the onset of T2DM [27]. The reduction in carbohydrate intake in a KD induces a state of nutritional ketosis, which alters the body's metabolism, leading to improved blood glucose levels and insulin sensitivity [28, 29]. In line with the present study, a systematic study by Huang *et al.* revealed that the ketogenic diet can improve insulin sensitivity in individuals with type 2 diabetes, with the most significant effect resulting from a ketogenic diet paired with exercise [30]. The study by Paoli *et al.* also confirms these findings and states that a ketogenic diet can improve blood sugar control and insulin sensitivity [31].

The reduction in HbA1c levels in the observation group supports the results of a study by Rafiullah *et al.,* which concluded that very low-carbohydrate ketogenic diets effectively reduce HbA1c in individuals with T2DM [32]. A recent systematic review and meta-analysis conducted by Zaki *et al.* [33] found that low carbohydrate (LCD) and KD positively impact glucose regulation in individuals with Type 2 Diabetes. Nevertheless, the analysis indicated that ketogenic diets demonstrate notably higher effectiveness in lowering HbA1c levels (− 1.45%) when compared to LCD (− 0.27%) [33].

The results of the present study showed that the ketogenic diet increases the serum level of GLP-1 in diabetic patients. GLP-1 is a hormone produced by the intestines that helps regulate blood sugar levels and stimu-

lates insulin secretion [34]. Widiatmaja *et al*. conducted a study to analyze the long-term effect of KD on the serum levels of adiponectin and IGF-1 in rats. The results showed that long-term KD increases serum adiponectin levels and does not affect serum IGF-1 levels [35]. This finding is contrary to the results of the present study, which could be due to the type of participants and the type of study. Since human studies on this parameter have not been conducted in people with a KD diet, it is necessary to investigate this matter further.

Finally, the present study showed that KD improves intestinal microbiota. KD improves *Bifidobacterium* and *Lactobacillus* levels and reduces *E. faecalis* and *E. coli* levels in the intestine. Previous studies have also shown that a very low-calorie ketogenic diet (VLCKD) can lead to significant changes in gut microbiota composition in drug-naïve patients with T2DM and obesity. One study compared the effects of VLCKD and a hypocaloric Mediterranean diet (MD) on gut microbiota in patients with T2DM and obesity. The results showed that the VLCKD group had more significant changes in gut microbiota composition [36]. The study of Paoli *et al*. also supports this idea and results [37]. Since the number of studies in this field is limited, more studies are recommended.

In conclusion, this study confirms that a ketogenic diet significantly outperforms standard dietary treatments for type 2 diabetes mellitus over six months. It more effectively lowers blood glucose levels, improves lipid profiles, reduces body weight and waist circumference, and beneficially alters gut microbiota. These findings highlight the ketogenic diet's potential as a superior dietary intervention for managing type 2 diabetes.

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Contributions of authors

All authors were involved in data collection, article design, interpretation of results, review, and manuscript preparation.

Conflict of interests

The authors declare no conflict of interest.

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REFERENCES

1. **Han Y, Kim D-Y, Woo J, Kim J**. Glu-ensemble: An ensemble deep learning framework for blood glucose forecasting in type 2 diabetes patients. Heliyon 2024;10:e29030.
2. **Sahu MK, Tiwari SP**. Epidemiology, pathogenesis and treatment of diabetes: A comprehensive review. World J Diabetes Res Pract 2024;1(1):1-9.
3. **Szablewski L**. Insulin resistance: the increased risk of cancers. Curr Oncol 2024;31(2):998-1027. *https://doi.org/10.3390/curroncol31020075"31020075*
4. **Yan Y, Wu T, Zhang M, Li C, Liu Q, Li F**. Prevalence, awareness and control of type 2 diabetes mellitus and risk factors in Chinese elderly population. BMC Public Health 2022;22(1):1382. *https://doi.org/10.1186/s12889-022-13759-9"12889-022-13759-9*
5. **Dludla PV, Mabhida SE, Ziqubu K, Nkambule BB, Mazibuko-Mbeje SE, Hanser S, Basson AK, Pheiffer C, Kengne AP**. Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress. World J Diabetes 2023;14(3):130-146. *https://doi.org/10.4239%2Fwjd.v14.i3.130"3.130*.
6. **Galdón Sanz-Pastor A, Justel Enríquez A, Sánchez Bao A, Ampudia-Blasco FJ**. Current barriers to initiating insulin therapy in individuals with type 2 diabetes. Front Endocrinol 2024;15:1-11. *https://doi.org/10.3389/fendo.2024.1366368"2024.1366368*

7. **Vlacho B, Rossell-Rusiñol J, Granado-Casas M, Mauricio D, Julve J**. Chapter 1 - Overview on chronic complications of diabetes mellitus. In: Mauricio D, Alonso N, editors. Chronic Complications of Diabetes Mellitus: Academic Press; 2024. p. 1-10.
8. **Mansour A, Mousa M, Abdelmannan D, Tay G, Hassoun A, Alsafar H**. Microvascular and macrovascular complications of type 2 diabetes mellitus: Exome wide association analyses. Front Endocrinol 2023;14:1143067. *https://doi.org/10.3389%2Ffendo.2023.1143067"2023.1143067*
9. **El Sayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA, on behalf of the American Diabetes Association.** 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care 2023;46(1):S19-S40 *https://doi.org/10.2337%2Fdc23-S002"002*
10. **Tourkmani AM, Alharbi TJ, Rsheed AMB, Alotaibi AF, Aleissa MS, Alotaibi S, Almutairi AS, Thomson J, Alshahrani AS, Alroyli HS, Almutairi HM.** A hybrid model of in-person and telemedicine diabetes education and care for management of patients with uncontrolled Type 2 diabetes nellitus: findings and implications from a multicenter prospective study. Telemedicine Reports 2024;5(1):46-57. *https://doi.org/10.1089/tmr.2024.0003"2024.0003*
11. **Garedow AW, Jemaneh TM, Hailemariam AG, Tesfaye GT**. Lifestyle modification and medication use among diabetes mellitus patients attending Jimma University Medical Center, Jimma zone, south west Ethiopia. Sci Rep 2023;13(1):4956. *https://doi.org/10.1038%2Fs41598-023-32145-y"-y*
12. **Firman CH, Mellor DD, Unwin D, Brown A**. Does a ketogenic diet have a place within diabetes clinical practice? Review of current evidence and controversies. Diabetes Ther 2024;15(1):77-97. *https://doi.org/10.1007%2Fs13300-023-01492-4" 13300-023-01492-4.*
13. **Zhu H, Bi D, Zhang Y, Kong C, Du J, Wu X, Wei Q, Qin H**. Ketogenic diet for human diseases: the underlying mechanisms and potential for clinical implementations. Signal Transduct Target Ther 2022;7(1):11. *https://doi.org/10.1038%2Fs41392-021-00831-w"-w*
14. **Masood W, Annamaraju P, Khan Suheb MZ, Uppaluri KR**. Ketogenic Diet. StatPearls. Treasure Island (FL): StatPearls Publishing LLC; 2024.
15. **Wu J, Yang K, Fan H, Wei M, Xiong Q**. Targeting the gut microbiota and its metabolites for type 2 diabetes mellitus. Front Endocrinol 2023;14:1-12. *https://doi.org/10.3389/fendo.2023.1114424"2023.1114424*
16. **Lin Y**. The role of ketogenic diet in gut microbiota. Highl Sci Eng Technol 2022;19:36-43.
17. **Koutentakis M, Kuciński J,** Świeczkowski **D, Surma S, Filipiak KJ, Gąsecka A**. The ketogenic effect of SGLT-2 inhibitors-beneficial or harmful? J Cardiovasc Dev Dis 2023;10(11):465. *https://doi.org/10.3390%2Fjcdd10110465"10110465*
18. **Sadat A**. Alarming surge in early-onset Type 2 diabetes: A global catastrophe on the horizon. Touch REV Endocrinol 2023;19(2):7-8. *https://doi.org/10.17925%2FEE.2023.19.2.5"2023.19.2.5*
19. **Committee ADAPP**. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care 2021;45(Supplement_1):S17-S38. *https://doi.org/10.2337/dc22-S002"002*
20. **Chandgude D, Tambat P, Tale V**. A comprehensive review on keto diet on management of Type 2 diabetes and obesity. J Chem Health Risks 2024;13(4):609-614.
21. **Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C**. Pathophysiology of Type 2 diabetes mellitus. Int J Mol Sci 2020;21(17):6275. *https://doi.org/10.3390%2Fijms21176275"21176275*
22. **Li S, Yuan S, Lin G, Zhang J**. Effects of a two meals-a-day ketogenic diet on newly diagnosed obese patients with type 2 diabetes mellitus: a retrospective ob-

servational study. Medicine (Baltimore). 2023;102(43):e35753. *https://doi.org/10.1097%2FMD.0000000000035753" 00000 00000035753*

23. **Zhou C, Wang M, Liang J, He G, Chen N**. Ketogenic diet benefits to weight loss, glycemic control, and lipid profiles in overweight patients with Type 2 diabetes mellitus: A meta-analysis of randomized controlled trails. Int J Environ Res Public Health 2022;19(16):10429. *https://doi.org/10.3390%2Fijerph191610429"191610429*
24. **Yuan X, Wang J, Yang S, Gao M, Cao L, Li X, Hong D, Tian S, Sun C**. Effect of the ketogenic diet on glycemic control, insulin resistance, and lipid metabolism in patients with T2DM: a systematic review and meta-analysis. Nutr Diabetes 2020;10(1):38. *https://doi.org/10.1038/s41387-020-00142-z"-z*
25. **Vidić V, Ilić V, Toskić L, Janković N, Ugarković D**. Effects of calorie restricted low carbohydrate high fat ketogenic vs. non-ketogenic diet on strength, body-composition, hormonal and lipid profile in trained middle-aged men. Clin Nutr 2021;40(4):1495-1502. *https://doi.org/10.1016/j.clnu.2021.02.028"2021.02.028*
26. **Patikorn C, Saidoung P, Pham T, Phisalprapa P, Lee YY, Varady KA, Veettil SK, Chaiyakunapruk N**. Effects of ketogenic diet on health outcomes: an umbrella review of meta-analyses of randomized clinical trials. BMC Medicine 2023;21(1):196. *https://doi.org/10.1186/s12916-023-02874-y"-y*
27. **Yang Q, Vijayakumar A, Kahn BB**. Metabolites as regulators of insulin sensitivity and metabolism. Nat Rev Mol Cell Biol 2018;19(10):654-672. *"https://doi.org/10.1038/s41580-018-0044-8"41580-018-0044-8*
28. **Dowis K, Banga S**. The potential health benefits of the ketogenic diet: A narrative review. Nutrients 2021;13(5):1654. *"https://doi.org/10.3390%2Fnu13051654"13051654*
29. **Yang Z, Mi J, Wang Y, Xue L, Liu J, Fan M, Zhang D, Wang L, Qian H, Li Y**. Effects of low-carbohydrate diet and ketogenic diet on glucose and lipid metabolism in type 2 diabetic mice. Nutrition 2021;89:111230. *"https://doi.org/10.1016/j.nut.2021.111230"2021.111230*
30. **Skow SL, Jha RK**. A ketogenic diet is effective in improving insulin sensitivity in individuals with Type 2 diabetes. Curr Diabetes Rev 2023;19(6):e250422203985. *"https://doi.org/10.2174/1573399818666220425093535"15733998186662204250935 35*
31. **Paoli A, Bianco A, Moro T, Mota JF, Coelho-Ravagnani CF**. The effects of ketogenic diet on insulin sensitivity and weight loss, which came first: the chicken or the egg? Nutrients 2023;15(14):3120. *"https://doi.org/10.3390%2Fnu15143120"15143120*
32. **Rafiullah M, Musambil M, David SK**. Effect of a very low-carbohydrate ketogenic diet vs recommended diets in patients with type 2 diabetes: a meta-analysis. Nutr Rev 2022;80(3):488-502. *"https://doi.org/10.1093/nutrit/nuab040"040*
33. **Zaki HA, Iftikhar H, Bashir K, Gad H, Fahmy AS, Elmoheen A**. A comparative study evaluating the effectiveness between ketogenic and low-carbohydrate diets on glycemic and weight control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Cureus 2022;14(5). *"https://doi.org/10.7759/cureus.25528"25528*
34. **Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, Fritsche A, Gribble F, Grill HJ, Habener JF, Holst JJ, Langhans W, Meier JJ, Nauck MA, Perez-Tilve D, Pocai A, Reimann F, Sandoval DA, Schwartz TW, Seeley RJ, Stemmer K, Tang-Christensen M, Woods SC, DiMarchi RD, Tschöp MH**. Glucagon-like peptide 1 (GLP-1). Mol Metab 2019;30:72-130. *"https://doi.org/10.1016%2Fj.molmet.2019.09.010"2019.09.010*
35. **Widiatmaja DM, Lutvyani A, Sari D, Kurniasari H, Meiliana I, Fasitasari M, Yamaoka Y, Rejeki P**. The effect of long-term ketogenic diet on serum adiponectin and insulin-like growth factor-1 levels in mice. J Basic Clin Physiol Phar-

macol 2021;33(5):1-11. *"http://dx.doi.org/10.1515/jbcpp-2021-0287"2021-0287*

36. Deledda A, Palmas V, Heidrich V, Fosci M, Lombardo M, Cambarau G, Lai A, Melis M, Loi E, Loviselli A, Manzin A, Velluzzi F. Dynamics of gut microbiota and clinical variables after ketogenic and mediterranean diets in drug-naïve patients with Type 2 diabetes mellitus and obesity. Metabolites 2022;12(11):1092. *"https://doi.org/10.3390%2Fmetabo12111092"12111092*

37. Paoli A, Mancin L, Bianco A, Thomas E, Mota JF, Piccini F. Ketogenic diet and microbiota: friends or enemies? Genes 2019;10(7):534. *"https://doi.org/10.3390/genes10070534"10070534*