



VERY-LOW-CARBOHYDRATE HYPOCALORIC DIET AND COFFEE INTAKE EXHIBIT ADDITIVE AND REINFORCING EFFECTS IN PREVENTION AND REVERSAL OF TYPE 2 DIABETES MELLITUS: PRELIMINARY EVIDENCE

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ABSTRACT

Increasing sedentary lifestyles fuel the rising incidence of type 2 diabetes mellitus, a major risk factor for memory loss, kidney failure and stroke. Of all dietary manipulations, only the hypocaloric intervention has acquitted itself as a credible and potent tool for the prevention and reversal of type 2 diabetes mellitus. Dietary lifestyle intervention or calorie restriction-mimetics have shown great promise in reversing omics signatures to normal in type 2 diabetes mellitus, dyslipidaemia and epilepsy. The modified hypocaloric ketogenic diet preserves beta-cell mass and suppresses the deleterious effects of hyperinsulinaemia as a result of high-carbohydrate indulgence. The very-low-carbohydrate ketogenic diet possesses additive effects with coffee intake at several levels in the brain and peripheral organs. They may synergistically upregulate the sensitivity and levels of the present major anti-insulin resistance treatments of insulin, insulin sensitizers, glucagon-like peptide-based agents and adiponectin. They may also co-operate with exercise to enhance higher cognitive function, upregulate adiponectin- and GLP-I-induced suppression of the advanced glycation endproducts (AGE)-receptor for advanced glycation endproducts (RAGE) axis and attenuate the selective leptin resistance (SLR) in the metabolic syndrome. Present report shows that habitual coffee intake and very-low-carbohydrate ketogenic diet most significantly ($P < 0.05$) prevented rise of selected factors of BMI, FBS, triglycerides and HbA1c in non-diabetics than VLCKD or coffee alone. The combination also most significantly reversed the rise of these factors in subjects with the insulin resistance state. The combination thus attests to its eligibility in the prevention and reversal of type 2 diabetes mellitus in Nigerian adults.

KEYWORDS: Hypocaloric, coffee, very-low-carbohydrate, prevention, reversal, type 2 diabetes mellitus.

INTRODUCTION

Dietary restriction of energy or calorie restriction reverses the progressive β -cell failure and insulin resistance characteristic of type 2 diabetes mellitus.^{[1][2]}

^[3] The weight-loss version of the ketogenic diet, very-low-calorie diet (VLCD), has been demonstrated to be a useful alternative in the treatment of the obese non-insulin dependent diabetes mellitus (NIDDM) patient.^[4] Increased energy intake or nutrient overload and positive energy balance are the culprits for insulin resistance through the production of obesity and/or increased diacylglycerol deposition in the liver and pancreas.^{[5][6][7]}

Recommended calorie intake

. Men, active women: 15 cal./lb

. Most women, sedentary men and adults over 55 years: 13 cal./lb

. Sedentary women, obese adults: 10 cal./lb

. Pregnant lactating women: 15 to 17 cal./lb

Thus, an overweight man who weighs 250 lb would need to eat 2,500 calories per day to maintain his weight. To lose 1 or 2 pounds per week, he should eat 1,500 to 2,000 calories per day. As weight is lost, the recommended calorie intake is recalculated.

FAO/WHO recommends 55% of carbohydrates in diets of normal healthy adults with adequate exercise. This dietary pattern may not be suitable for sedentary subjects. Also, the favourable effect of substituting monounsaturated fat for saturated fat is lost in individuals consuming more than 37% of energy as fat.^[8]

These and other workers have recommended that saturated fat intake should be less or about 7% of total energy intake.^[9] Diet and physical activity are critically important in the management of the ABCs (A1c, blood pressure and cholesterol) of type 2 diabetes mellitus.^{[10][11]}

Calorie restriction

Reduced calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasise and prevent diabetes.^{[12][13]} All have been shown to improve fasting insulin levels and lipid-related risk factors in man,^{[14][15]} and experimental animals.^{[13][16][17][18]} Calorie restriction alters hepatic lipid droplet proteome and prevents metabolic aging caused by mutant SIRT1 function in adipose tissue. Although fasting helps to reverse diabetes,^[19] there is the caveat that cyclical calorie restriction and intermittent access to sugar solution plus high glycaemic foods may result in opioid-like forebrain neural alteration and dependency in rodents.^[17]

Energy restriction (as part of very-low-energy diet, VLED) and exercise both facilitate weight loss in overweight and obese subjects and reduce symptoms of the metabolic syndrome.^[20] Calorie restriction, glucose restriction and moderate physical activity enhance mitochondrial activity and increases reactive oxygen species (ROS) that ultimately induce and adaptive response (mitohormesis) to improve stress resistance.^[21]

Dietary strategies to prevent and reverse type 2 diabetes mellitus

Very-low carbohydrate diet versus traditional isocaloric low-fat high carbohydrate diet: Isocaloric low-fat high-carbohydrate diets have shown poor results for weight loss,^{[22][23][24]} and failed to curb the type 2 diabetes epidemic.^[25] Dietary carbohydrate restriction which enhances ketogenesis,^{[26][27][28]} induces a unique metabolic state positively affecting atherogenic dyslipidaemia, fatty acid partitioning and metabolic syndrome.^[23] Dietary carbohydrate, which is more dangerous than dietary fat in increasing *de novo* lipogenesis,^[29] affects the relation between dietary intake of saturated fat and circulating levels. Dietary carbohydrate has been shown to modulate lipolysis, lipoprotein assembly and processing. Carbohydrate restriction might control the survival/death decision of neurons via partitioning of fatty acids between ketogenesis and toxic ceramide synthesis.^[30] Less than 20 g/day of carbohydrate induce ketosis, cause great reduction in HbA1c, increase HDL-cholesterol and may reverse type 2 diabetes.^[31] Thus carbohydrate restriction has been proposed as the first approach in diabetes management.^[24] The digestible report by these workers highlighted that the beneficial effects of carbohydrate restriction accrue even without weight loss, though it remains the best for weight loss. The pescetarian type of semi-vegetarianism coupled with restriction of carbohydrates, sugar-sweetened beverages and sugary

fruits should satisfy need for essential nutrients for subjects on a hypocaloric very-low-carbohydrate diet and prevent the incurrence of peptic ulcers, sleeplessness and malnutrition.^{[29][32]}

The role of protein intake

Increasing protein of a reduced energy diet without severe carbohydrate restriction does not affect the ability of a reduced energy diet to prevent NIDDM.^[14] Higher vegetable low-carbohydrate diet has been found to be associated with lower all-cause and cardiovascular mortality than animal low-carbohydrate diet.^[33] In the same vein, a hypocaloric low-fat vegan diet with the carbohydrates mostly from higher fibre and non-starch polysaccharides (NSP) prevents and reverses diabetes and improves glycaemic control and cardiovascular risk factors.^{[8][34][35]} Resistant starch in NSP may contribute in reversing NIDDM and increasing β -cell mass. Restriction of protein or essential amino acids (which activate the mammalian target of rapamycin (mTOR) extends healthspan.^{[36][37][38]}

The detrimental role of a high-carbohydrate diet

Source and type of carbohydrate are more important than quantity in terms of diabetes prevention.^{[8][37]} Low intake of dietary fibre, non-starch polysaccharides and low-glycaemic index foods increases diabetes risk. Uncontrolled intake of high-carbohydrate diet has detrimental effects,^[39] and carbohydrates may not be essential for existence.^[26] It increases the level of advanced glycation end-products (AGE) in crucial plasma proteins concerned with fat, cholesterol, oxygen transport and insulin signaling. This may lead to cholesterol deficiency in neurons via attenuating astrocyte to neuron cholesterol transport important for prevention of Alzheimer's disease (AD).^[40] Progressively, there is impaired glutamate signalling, increased oxidative damage, mitochondrial and lysosomal dysfunction and increased risk of microbial infection. High-carbohydrate is associated with persistently high insulin levels which is a culprit for insulin resistance and cancer.^[41] Whereas high-fat and high-carbohydrate diets may cause central neuronal apoptosis,^{[39][42]} and increase dopamine release in the nucleus accumbens, it is only the latter that has been associated with withdrawal syndrome.^[43]

An ascendant negative impact of alcohol, free sugars, high-carbohydrate indulgence and, in susceptible persons, cannabis on cardiometabolic health in emerging and industrialised economies has been observed.^[44] These various factors may intersect and reinforce to explain why food craving behaviour is linked to drug craving behaviour and the phenomenon of 'addiction transfer' common after bariatric surgery for obesity.^{[45][46]}

Beneficial effects of a very-low-carbohydrate ketogenic diet (VLCKD)

There is increase of brain and heart mitochondria after a ketogenic diet.^{[47][48]} The low-carbohydrate ketogenic

diet increases GABA levels while decreasing glutamate levels. It is anti-inflammatory and has anti-oxidant effects thus attenuating chronic inflammatory diseases of the CNS such as epilepsy and AD.^[49] Thus the pro-cognitive effects of coffee may reinforce the beneficial effects of VLCKD to enhance memory function which is a problem in the elderly and in the chronic diabetic. The ketone body, β -hydroxy butyrate, which is primarily produced in the liver, acts on its receptors to reduce sympathetic tone and inhibit histone deacetylase I (HDAC I). In contrast to lean mice, obese or diabetic mice show improved glucose tolerance and insulin sensitivity.^[50] Ketone bodies lower the serum ratio of IGF to insulin-like growth factor binding protein (IGF/IGFBP3) that has been associated with the metabolic syndrome and cancer. Ketone bodies increase AMPK activity and enhance PGC1- α/β signalling to target genes such as PPAR- α and the anti-oxidant nuclear respiratory factor (NRF) I/2.^{[50][51]} There is co-operation between AMPK and PPAR- α which is pro-ketogenic in the control of energy homeostasis.^[52] The low-carbohydrate diet, enhanced leptin and insulin anorexigenic activity, upregulation of CCK/ghrelin ratio, increased n-acylphosphatidyl ethanolamine by the very-low-calorie carbohydrate ketogenic diet reduce appetite to cause lower food intake. Cellulose and hemicellulose from resistant starch in non-starch polysaccharides enhance short-chain fatty acids level which upregulates secretion of GLP-I from the gut. Their bulk also prevent constipation, a problem in the elderly. The upregulation of GLP-I by the VLCKD may be additive with the effect of coffee in enhancing GLP-I levels. GLP-I based therapies, which possess pro-survival systemic hypoglycaemic and non-glycaemic actions, increase adiponectin levels, a critical insulin sensitizer.^[53] On the contrary, a high-fat ketogenic diet causes hepatic insulin resistance in mice, despite increasing energy expenditure and preventing weight gain.^[7] Long-term high-fat ketogenic diet may also cause glucose intolerance with a reduction in pancreatic β -cell mass.^{[54][55]} Also and paradoxically, a high ketogenic ratio diet (high-fat diet) may alter gut microbiota via increasing *Firmicutes/Bacteroidetes* ratio and negatively impact cardiometabolic disease.^{[56][57][58]} This may reflect the new-found link between gut microbiota and obesity,^[59] and the increasing relevance of pre-biotics and diets with low ketogenic ratios].

Contra-indications to the ketogenic diet

Ketosis is contra-indicated in subjects on high-intensity metabolic conditioning. Investigators recently demonstrated with the Geometric Framework studies that a carbohydrate-protein ratio of 16: 1 extends lifespan in cold climes and in subjects actively exercising. In this dietary pattern, NSP, resistant starch and low-glycaemic index foods are the recommended sources of carbohydrates. Induction of ketosis is also contra-indicated in subjects wanting to get pregnant. The mammalian target of rapamycin is necessary for fetal placental transport of nutrients and muscle growth.^{[60][61]}

The ketogenic diet and coffee both inhibit the mammalian target of rapamycin and this may explain the decrease in muscle mass (sarcopenia) that may accompany their use. Pescetarianism with consumption of marine fish may offset this potential side-effect of the ketogenic diet. Induction of ketosis is also contra-indicated in type I diabetes where it may induce hyperketonaemia; and in porphyria and pyruvate decarboxylase deficiency.

Beneficial effects of habitual coffee consumption

Coffee consumption, apart from decreasing leptin resistance, increasing adiponectinergic transmission and enhancing central insulin signalling, increases plasma ketones in a dose-dependent manner.^[62] It is also beneficial in salt-sensitive hypertension associated with insulin resistance. Hyperleptinaemia or the selective leptin resistance (SLR) in the metabolic syndrome is also a risk factor for high blood pressure in the high-fat induced obese and elderly.^{[63][64][65][66]} There is ventricular contractile dysfunction in obesity. Toxic isoforms of ceramide sensitises the cardiac depressive effects of obesity-related hyperleptinaemia.^[67] Thus, habitual coffee consumption could enhance the ketogenic effects of medium-chain triglycerides as well as be additive with the ketogenic effects of the hypocaloric very-low-carbohydrate diet on brain function and cardiac efficiency.^[68]

AIM OF THE STUDY

The aim of the study was to investigate the effect of a hypocaloric very-low-carbohydrate ketogenic diet and coffee consumption on the prevention and reversal of type 2 diabetes mellitus with some parameters of the insulin resistance syndrome. Subjects with or without type 2 diabetes were employed and compared to control subjects.

Methods

This prospective study was done at Department of Pharmacology, AAU, Ekpoma, Oriaifo Medical Centre, Uromi and Oseghale Oriaifo Medical Centre, Ekpoma in 2016. Patients' informed consent was obtained in writing and study was approved by the Ethical Committee of AAU's College of Medicine, Ekpoma and of Oriaifo Medical Centre (Proposed Oriaifo Medical University), Uromi. 20 patients (45-80 years old) of either sex participated in either arm of the study with similar number of controls.

Prevention of obesity and type 2 DM

20 patients of either sex participated in the study with similar number of controls. Coffee intake was 2-3 cups of black caffeinated coffee a day. The bitterness of black coffee may provoke long-lasting decrease in ghrelin levels,^[69] and contribute to increasing secretion of the incretin hormone, GLP-I.^[70] The intake was tailored to individual needs in order to avoid side-effects since some subjects tolerated higher intake than others. Subjects

started the hypocaloric very-low-carbohydrate ketogenic diet at the same time.

Reversal of type 2 DM

In this arm, participants either had prediabetes or were type 2 diabetic patients already on treatment. The number of controls, test patients and dietary regimens were similar to the above arm of the study.

Body Mass Index (BMI), fasting blood sugar (FBS), triglycerides and glycated haemoglobin (HbA1c) were estimated after a week of the initiation of the combined regimen and repeated after 6 months, 1 year and 1 year 6 months. Laboratory studies were done at the Clinical Chemistry Laboratories, Oriaifo Medical Centre, Uromi and Irrua Specialist Teaching Hospital, Irrua.

Inclusion criteria

For the first arm of the study, healthy adults without obesity volunteered and had BMI of 20-29 kg/m². Overweight subjects took part in the second arm, where patients who participated were those fit to tolerate the hypocaloric very-low-carbohydrate ketogenic diet after thorough explanation of the accruable benefits and possible side-effects. For example, they were informed that there might some weakness during the period of keto-adaptation when the brain gets used to reliance on the available glucose and relies on ketones for ATP generation. The peripheral organs mostly then depends on fatty acids for energy. The prediabetic patients had FBS of 100-124 mg/dl. Moderate heart failure and hypertensive patients also participated.

Table I: Example of some recommended hypocaloric very-low-carbohydrate Nigerian diet RECOMMENDED FOOD INTAKE.

Breakfast	Lunch	Dinner
1-2 cups of black coffee + Half-piece of avocado pear or 3 Nigeria pears or ¼ of coconut or 2 serving of vegetables	0-1 cup of black coffee + Half-piece of avocado pear or 3 Nigeria pears or ¼ of coconut or 1 serving egusi melon soup or 2 serving of vegetables or 1-2 pieces of water yam 5-15 walnuts or 10-20 groundnuts	1-2 pieces of fresh -water (<u>riverine</u>) fish with soup or 1 piece of chicken with soup + 3-4 spoons of beans or 2 servings of vegetables.

The guide may provide 600-850 calories/day.

Dietary practices vary from community to community and management of type 2 DM may now be metamorphosing into personalised medicine. So, the above dietary recommendation is only advisory.

Table 2 shows the comparative nutrient content of common Nigerian staple food items. Yams may contain less sugar, carbohydrates and fat than cassava. Yams, cassava and sweet potato are calorie-dense and charcoal-roasting of yams and frying of sweet potatoes transform them from low-glycaemic to high-glycaemic index food items. Sweet-potatoes (*Ipomoea batatas*) contain relatively high concentration of beta-carotene, anthocyanins and polyphenols with alpha-glucosidase and alpha-amylase activity,^[71] and it may particularly benefit the non-obese in preventing post-prandial hyperglycaemia. Linoleic acid amongst the polyunsaturated fatty acids (PUFAs) in egusi melon seed, which possesses lower carbohydrate content than groundnut, may impact favourably on hypercholesterolemia, cardiomyopathy and

atherosclerosis (ajpheart.physiology.org.2005; ijcrbp.com.2015).

Exclusion criteria

For both arms, morbidly obese subjects with BMI of > 39 kg/m² were excluded. Children, young adults and pregnant women were excluded. Also excluded were severely hypertensive and congestive heart failure patients. Patients with stroke, liver failure, kidney failure patients on regular dialysis and those on long-term steroids were also excluded.

Outcome

The primary outcomes observed were effect of the regimen on insulin and metformin requirements, HbA_{1c}, BMI, FBS and triglyceride levels after 1 year 6 months. 5 participants in the first arm and 4 patients withdrew from the study either because they could not get used to the regular coffee intake or adhere to a hypocaloric very-low-carbohydrate diet.

Statistical analysis

Analysis was done using SPSS version 19.0 instrument. One-way ANOVA was applied followed by DMR as *post-hoc* test. Mann-Whitney non-parametric test was used when comparing the means of two samples. The difference was considered to be significant at $P < 0.05$.

Table 2: Comparative Nutrient Content of Common Nigerian Staple Foods

Nutrient content of major staple foods per 100g portion ^[42]												
Nutrient component:	Maize / Corn ^[A]	Rice (white) ^[B]	Rice (brown) ^[I]	Wheat ^[C]	Potato ^[D]	Cassava ^[E]	Soybean (Green) ^[F]	Sweet potato ^[G]	Yam ^[Y]	Sorghum ^[H]	Plantain ^[Z]	RDA
Water (g)	10	12	10	13	79	60	68	77	70	9	65	3000
Energy (kJ)	1528	1528	1549	1369	322	670	615	360	494	1419	511	8368–10460
Protein (g)	9.4	7.1	7.9	12.6	2.0	1.4	13.0	1.6	1.5	11.3	1.3	50
Fat (g)	4.74	0.66	2.92	1.54	0.09	0.28	6.8	0.05	0.17	3.3	0.37	
Carbohydrates (g)	74	80	77	71	17	38	11	20	28	75	32	130
Fiber (g)	7.3	1.3	3.5	12.2	2.2	1.8	4.2	3	4.1	6.3	2.3	30
Sugar (g)	0.64	0.12	0.85	0.41	0.78	1.7	0	4.18	0.5	0	15	
Calcium (mg)	7	28	23	29	12	16	197	30	17	28	3	1000
Iron (mg)	2.71	0.8	1.47	3.19	0.78	0.27	3.55	0.61	0.54	4.4	0.6	8
Magnesium (mg)	127	25	143	126	23	21	65	25	21	0	37	400
Phosphorus (mg)	210	115	333	288	57	27	194	47	55	287	34	700
Potassium (mg)	287	115	223	363	421	271	620	337	816	350	499	4700
Sodium (mg)	35	5	7	2	6	14	15	55	9	6	4	1500
Zinc (mg)	2.21	1.09	2.02	2.65	0.29	0.34	0.99	0.3	0.24	0	0.14	11
Copper (mg)	0.31	0.22		0.43	0.11	0.10	0.13	0.15	0.18	-	0.08	0.9
Manganese (mg)	0.49	1.09	3.74	3.99	0.15	0.38	0.55	0.26	0.40	-	-	2.3
Selenium (µg)	15.5	15.1		70.7	0.3	0.7	1.5	0.6	0.7	0	1.5	55
Vitamin C (mg)	0	0	0	0	19.7	20.6	29	2.4	17.1	0	18.4	90
Thiamin (B1)(mg)	0.39	0.07	0.40	0.30	0.08	0.09	0.44	0.08	0.11	0.24	0.05	1.2
Riboflavin (B2)(mg)	0.20	0.05	0.09	0.12	0.03	0.05	0.18	0.06	0.03	0.14	0.05	1.3
Niacin (B3) (mg)	3.63	1.6	5.09	5.46	1.05	0.85	1.65	0.56	0.55	2.93	0.69	16
Pantothenic acid (B5) (mg)	0.42	1.01	1.49	0.95	0.30	0.11	0.15	0.80	0.31	-	0.26	5
Vitamin B6 (mg)	0.62	0.16	0.51	0.3	0.30	0.09	0.07	0.21	0.29	-	0.30	1.3
Folate Total (B9) (µg)	19	8	20	38	16	27	165	11	23	0	22	400
Vitamin A (IU)	214	0	0	9	2	13	180	14187	138	0	1127	5000
Vitamin E, alpha-tocopherol	0.49	0.11	0.59	1.01	0.01	0.19	0	0.26	0.39	0	0.14	15

(mg)												
Vitamin K1 (µg)	0.3	0.1	1.9	1.9	1.9	1.9	0	1.8	2.6	0	0.7	120
Beta-carotene (µg)	97	0		5	1	8	0	8509	83	0	457	10500
Lutein+zeaxanthin (µg)	1355	0		220	8	0	0	0	0	0	30	
Saturated fatty acids (g)	0.67	0.18	0.58	0.26	0.03	0.07	0.79	0.02	0.04	0.46	0.14	
Monounsaturated fatty acids (g)	1.25	0.21	1.05	0.2	0.00	0.08	1.28	0.00	0.01	0.99	0.03	
Polyunsaturated fatty acids (g)	2.16	0.18	1.04	0.63	0.04	0.05	3.20	0.01	0.08	1.37	0.07	

Source: Nutrients Data Laboratory. USDA.

RESULTS

Table 3: Effect of coffee and VLCKD ON BMI, FBS, TRIGDYCERIDES AND HbA1C compared to control in prevention of TZDM

	0				6 MONTHS				1 YEAR				1 ½ YEAR			
	Contro	Cof.	VLC	Comb	Contro	Cof.	VLC	Comb	Contro	Cof.	VLC	Comb	Contro	Cof.	VLC	Comb
BM	26.15	25.45	26.13	28.11	28.11	25.22	25.12	25.01	34.42	24.90	24.89	24.30	36.20	24.82	24.75	23.55*
Kg/M ²	+2.20	+2.10	+2.35	+2.44	+3.10	+2.01	+1.99	+1.50	+1.15	+2.20	+1.15	+1.06	+2.2	+0.88	+2.09	+1.62
FBS	100.0	100.1	99.8	99.7	110.20	93.76	92.07	90.05	126.00	98.01	87.66	86.84	128.20	88.11	86.22	85.44
Mg/dL	+2.50	+3.99	+2.87	+2.55	+1.50	+5.11	+5.22	+3.11	+2.20	+1.07	+2.20	+3.41	+4.45	+3.10	+1.11	+2.20
Triq.	98.50	98.31	97.20	97.25	99.31	97.70	97.15	96.05	115.30	92.11	96.75	95.85	120.12	96.54	95.44	94.62
Mg/dL	+1.11	+2.20	+5.5	+6.40	+1.30	+1.55	+2.20	+4.44	+2.1	+2.00	+1.12	+2.03	+5.40	+2.2	+1.90	+2.2
HBAIC	5.50	5.62	5.56	5.54	5.89	5.54	5.51	5.48	6.45	5.51	5.47	5.42	6.71	5.51	5.35	5.33
	+1.5	+4.10	+1.2	+3.10	+2.2	+1.99	+2.10	+3.30	+3.2	+2.2	+3.00	+2.03	+1.2	+2.80	+2.00	+2.70

Table 3: In control subjects, there was significant ($P < 0.05$) progression to prediabetes in 1^{1/2} years. Coffee + VLCKD most significantly (DMR) ($P^{***} < 0.05$) decreased HbA1c, Triglycerides, FBS and BMI than either VLCKD or Coffee alone.

Table 4: EFFECT OF COFFEE AND VLCKD ON BMI, FBS, TRIGLYCERIDES AND HBAIC COMPARED TO CONTROLS IN THE REVERSAL OF TZDM

	0				6 MONTHS				1 YEAR				1 ½ YEAR			
	Contro	Cof.	VLC	Comb	Contro	Cof.	VLC	Comb	Contro	Cof.	VLC	Comb	Contro	Cof.	VLC	Comb
BMI	36.77	36.44	37.04	136.65	36.79	30.14	27.05	25.44	37.22	30.06	27.12	25.01	37.81	30.01	27.22	24.55
Kg/M ²	+1.98	3.11	+1.66	+1.55	+2.05	+1.12	+2.11	+3.45	+2.44	+4.42	+1.155	±	+3.00	+4.44	+3.34	+1.12
FBS	190.55	180.95	180.76	180.55	200.15	103.99	102.15	99.34	210.66	103.5	95.55	91.44	220.5	98.55	90.03	85.66
Mg/dL	+2.88	+3.34	+4.00	+5.55	+3.11	+4.51	+5.55	+2.11	+4.12	+2.66	+4.88	+5.11	+3.66	+4.41	+1.12	+4.40
Triq	150.42	145.22	150.00	149.44	150.60	98.66	86.54	80.91	170.42	94.12	84.22	80.66	170.66	90.41	81.91	81.36

Mg/dL	+1.66	+3.11	+2.99	+3.66		+4.20	+5.11	+3.44	+5.20		+2.11	+4.20	+2.00	+3.22		+1.84	+1.05	+2.22	+1.69
HbA1C	9.88	10.05	11.04	11.11		10.85	9.01	8.84	7.25		11.01	8.89	6.60	6.45		11.05	6.91	6.41	6.05
	+2.51	+1.11	+3.31	+4.12		+2.12	+5.40	+4.41	+1.66		+2.34	+4.40	+3.44	+2.21		+1.09	+3.13	+1.47	+1.13

Table 4: In control subjects, HbA1C an indication of microvascular and macrovascular complications significantly ($P < 0.05$) increased after the study period. The combination of VLCKD and coffee most significantly (DMR) ($P^{***} < 0.05$) decreased HbA1C, BMI, FBS and triglycerides to normal values.

Results show that significant responses were observed after 6 months but most significant responses occurred at 1 year 6 months. A significant percentage of control subjects in the first arm were pre-diabetic at the end of the study period whereas the most protective diet in terms of extent of decrease in glycated haemoglobin was the combination of VLCKD and coffee. HbA1c levels were decreased below pre-test levels.

In the second arm, the dietary combination of coffee and VLCKD was most significant in reversing BMI, FBS, triglycerides to normal, and HbA1c to pre-diabetic level, at 1 year 6 months.

DISCUSSION

Report demonstrates that habitual coffee (caffeinated or decaffeinated) consumption and the very-low-carbohydrate ketogenic diet more significantly decrease BMI, FBS, triglycerides and glycated haemoglobin (HbA1c) levels than either alone thus indicating additive and reinforcing effects. In the Prevention arm, the combination brought the BMI level down to about 23 Kg/M², a level recommended by previous workers.^[8] Weight management is an important part of diabetes care (American Diabetes Association (2011). Present study extends our earlier report on the benefits of coffee intake on the reversal of some risk factors for type 2 diabetes mellitus such as salt-induced hypertension most prevalent in Blacks,^[72] and that calorie restriction was a *sine qua non* for this. Fasting, low-carbohydrate diet and even coffee may induce low-level ketonaemia which must be distinguished from the hyperketonaemia of type 1 diabetes mellitus. Coffee, by enhancing appetite suppression and exercise performance, may aid in the transition from an isocaloric ketogenic diet to the induction and compliance with a very- low-calorie (hypocaloric) carbohydrate ketogenic diet. Habitual coffee consumption will enhance the effect of VLCKD in the attainment of sufficient weight loss necessary for type 2 diabetes mellitus prevention and reversal.^{[73][74]} Moreover, VLCKD – and coffee – induced ketone body (β -hydroxybutyrate) upregulation may reduce sympathetic tone which is upregulated in type 2 diabetes mellitus by antagonising G protein-coupled receptor -41 which promotes secretion of leptin.^[75]

The relatively affluent citizens (some malnourished from birth) in emerging economies of Africa may be under a deluge of ‘cheap’ carbohydrate and animal-fat foods (www.pri.org). This, as a cause of obesity, may have inverted encouragement from misplaced government food policy which also allows misleading advertisements concerning food, alcohol and even cigarettes (*A report to Agriculture and Agri-Food, Canada; Food Value Chain Bureau. 2004*).

As highlighted by previous workers, nutrient overload-induced glucolipotoxicity caused by intake of the wrong type of carbohydrates, wrong type of fat and wrong type of proteins and lack of physical exercise contribute

significantly to the unabated pandemic of type 2 diabetic mellitus in adulthood,^[76] and its associations such as hypertension and non-alcoholic fatty liver disease. Obesity and high BMI levels are risk factors for type 2 diabetes, hypertension and dyslipidaemia.^[77] Dietary lifestyle intervention or calorie restriction-mimetics such as metformin and sitagliptin have shown greater effect than other pharmacological agents in reversing the deviated transcriptomic and physiological markers of type 2 diabetes mellitus, dyslipidaemia and epilepsy to normal.^{[78][79][80]}

Although some workers have not found significant association between coffee and HbA1c,^[81] other reports point to the salutary effects of its consumption on the progression of HbA1c among prediabetic individuals which is confirmed by present report.^[82] HbA1c (early glycation endproduct) is an adduct of proteins and reversible early glycosylation products which is used for the assessment of diabetic control. [United States Food and Drug Administration, 2008]^{[83][84]} The chorogenic acid, an important component of the coffee matrix, decreases HbA1c while increasing adiponectin levels.^[85] Adiponectin, an adipocytokine, has anti-diabetic and insulin-sensitizing effects.^[86] While the level of adiponectin is attenuated by high-carbohydrate, high-fat diets and obesity,^[87] it is upregulated by calorie restriction and physical exercise. Thus both coffee and VLCKD could have additive effects in elevating adiponectin levels and decreasing HbA1c levels to positively impact cardiovascular risk factors in type 2 diabetics. HbA1c level of < 7% is beneficial for cardiovascular outcome (AHA). Workers have demonstrated that VLCKD has a great effect in reversing glucose and HbA1c levels in type 2 diabetics to normal or to prediabetic levels, an effect more significant than that induced by VLCD, a study corroborated by present report.^[24]

Ketosis as well as low-carbohydrate diet upregulate adiponectin levels,^{[88][89]} and decrease markers of vascular stress. Adiponectin is inversely correlated with glycosylated haemoglobin,^[90] and would aid in the identification of high-risk individuals for diabetes. Adiponectin has been proven to have a significant protective role against the development of type 2 DM and also to display beneficial effects in persons with or without insulin resistance.^[91]

Pro-inflammatory pathways and hyperglutamatergic excitotoxicity are attenuated by calorie restriction-induced ketogenesis.^{[92][93]} Calorie restriction reduces vesicular glutamate release and enhances glutamate conversion to GABA while glucose restriction activates T_{ATP} channels in the CNS.^[92] Caffeine interacts with adenosine A_{2A} receptor and with glutamate receptor genotype to decrease hyper- glutamatergic excitotoxicity,^[94] while chlorogenic acid decreases oxidative and inflammatory stress.^[95] Thus, both the hypocaloric very-low-carbohydrate ketogenic diet and

habitual coffee intake decrease the simplified excitotoxic index of glutamate/GABA.

There is a close relation between the amount of red cell HbA1c and Hb-AGE in diabetic subjects although the diagnostic role of Hb-AGE has not been clarified. AGE represents, not just a measure of glycaemia, but cumulative metabolic burden, oxidative and inflammatory stress. AGE (which signals to RAGE and HMGBI) and hyperglycaemia-induced reactive oxygen species upregulate the AGE-RAGE axis to cause perturbations in various organ systems.^[96] RAGE, a pro-inflammatory and pro-fibrotic receptor and also a receptor for amyloid beta protein, is essential for activation of NF-kappaB and for the complications of DM,^[97] particularly diabetes-induced atherosclerosis and vasculopathy.^{[98][99]} The calorie restriction-mimetics, metformin, GLP-I analogues/enhancers such as sitagliptin and factors that increase adiponectin signalling such as habitual coffee intake may down-regulate the AGE-RAGE axis to decrease endothelial stress. In fact, sitagliptin downregulates COX-2 and attenuates endothelium-dependent contractions through the activation of GLP-I R/AMPK-alpha-/UCP2 signaling in renal arteries in hypertension.^[100] The anti-atherothrombotic and vaso-relaxant effects of sitagliptin may be adiponectin- and endothelial nitric oxide-dependent.^{[101][102]} Dietary lifestyle interventions such as coffee and VLCKD that upregulate the adiponectin and GLP-I signalings which intersect at several levels in the prevention and reversal of type 2 diabetes and its complications thus stand to down-regulate the distorted AGE-RAGE signalling in type 2 diabetes associated hypertension, chronic kidney disease, AD and accelerated atherosclerosis.^[103]

VLCKD and coffee could contribute to attenuating inflammatory and para-inflammatory diseases, enhancing cytoprotection, neuroprotection, vasculoprotection, cardioprotection and renoprotection. For example, both coffee intake and VLCKD could additively upregulate GLP-I and its analogues/enhancers which retard the progress of chronic diabetes-related neurodegenerative, cardiovascular and kidney diseases.^{[104][105][106]} Workers have demonstrated that the low-carbohydrate ketogenic diet independently reverses diabetic nephropathy in mice,^[107] present in 20-40% of type 2 diabetics which can culminate in end-stage renal disease (ESRD) or CDK stage 5 characterised by fibrosis. Our work with low-dose sitagliptin in a few subjects has shown that it decreases albuminuria, an early risk factor for CKD, in diabetic patients compared to controls which confirms previous studies on the renoprotective and diuretic effects of GLP-I based therapies.^{[108][109]} Linagliptin ameliorates fibrosis in streptozotocin-induced diabetic mice.^[110] Not the least, the diuretic, coffee enhances exercise performance which enhances adiponectin release and thus offsets the possible negative but disputed impact of VLCKD on physical performance.^{[111][112]}

In conclusion, the combination of coffee and VLCKD promises to be a priceless tool to be reckoned with in the prevention and reversal of T2DM, especially in our communities where high-carbohydrate intake is the rule rather than the exemption.

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