THERAPEUTIC ACTION OF KETOGENIC ENTERAL NUTRITION IN OBESE AND OVERWEIGHT PATIENTS: A RETROSPECTIVE INTERVENTIONAL STUDY

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Abstract

Background: Ketogenic Enteral Nutrition (KEN™) is a modification of Blackburn's protein-sparing modified fast, using a hypocaloric, ketogenic liquid diet. The study is about Ketogenic enteral nutrition (KEN) in overweight and obese patients receiving short treatment of the nutritional solution as 24-hour infusion. It is a retrospective analysis that examines safety, weight loss and body composition changes after three sequential 10-days cycles of KEN therapy. **Methods:** Anthropometric and bio-impedance data from 629 patients who underwent KEN were collected before and after completing a ten-day cycle. The study focuses on the change in outcomes from the first cycle to the second cycle and from the first cycle to the third cycle. The following outcomes were explored: weight, waist circumference, BMI, fat mass, lean mass, dry lean mass, phase angle, wellness marker, water mass as a percentage of total body weight. Statistical tests were used to test for significant differences between paired cycle 1 and cycle 2 outcomes and also between paired cycle 1 and cycle 3 outcomes. For normally distributed outcomes, the paired t-test was used. Whereas for skewed outcomes, the Wilcoxon signed-ranks test was used. Scatter plots were used to plot percentage of excess weight loss against phase angle. The Pearson's correlation coefficient was calculated. Regression analysis for the outcome percent change in weight from cycle 1 to cycle 2 for phase angle and basal metabolic rate (BMR)/ Weight ratio as predictors was carried out. **Results:** The results suggested significant changes for all analyzed parameters. There were significant decreases in weight, waist circumference, BMI, fat mass, lean mass, dry lean mass and phase angle. Quantitative changes in lean mass and dry lean mass were minor changes with respect to changes in fat mass. There was also a statistically significant increase in water mass as a % of total body weight and wellness marker from cycle 1 to cycle 3.

26 The Pearson's correlation coefficients r=0.18, p=0.004 and r=22, p=0.04 indicated

27 changes in cycle 1 and cycle 3 in percentage of weight excess to be significantly,

28 positively correlated to phase angle. The multivariate linear regression model showed

29 that for a 1 unit increase in BMR / weight there was a 3.3 percent decrease in percent

30 change in weight. KEN treatment was overall well tolerated. Long term results need

31 to be explored in further controlled studies . **Conclusions** KEN treatment is safe, well

32 tolerated and results in rapid fat loss without detriment to dry lean mass

33 Introduction

34 The global health burden of obesity continues to rise despite improved public

35 awareness of the importance of a healthy diet and regular exercise (1-3). Current

36 treatment options for weight reduction include dietary measures, pharmacotherapy,

37 endoscopic techniques and bariatric surgery. These are limited on the one hand by

38 efficacy and long-term sustainability and on the other hand by safety and

39 accessibility to the general public (4). Bariatric surgery is a valid therapeutic option

40 (5) however inherently invasive and it should not be the first port of call after the

41 failure of simple dietary measures (6, 7). Many of the currently available dietary

42 strategies have not been shown to produce selective fat loss without a significant

43 change in dry lean mass (4).

44 Dietary interventions that can produce weight reduction of the order of 5-10% of total

45 body weight have been shown to reduce obesity-related morbidity (8-12).

46 Ketogenic Enteral Nutrition (KEN™) is a protein-sparing modified fast that has been

47 developed in order to achieve rapid, safe, selective fat loss (13-16). Research

48 studies have challenged the notion that ketogenic diets are harmful and demonstrate

49 no loss of aerobic performance in athletes as well as obese individuals (18,19).

50   Lessons learnt from these studies suggest providing electrolyte and fluid

51   replacement to counteract the natriuretic and kaliuretic effects of a ketogenic diet,

52   together with adequate protein (0.9-1.2g/kg ideal body weight) can be safely

53   administered to patients for long periods of time without adverse effect (20). Previous

54   randomized controlled trials have demonstrated early satiety and significant weight

55   loss using a low-carbohydrate ketogenic diet over a six- to twelve-month period with

56   long-term safety and with preservation of lean mass (21-23).

57   On the basis of these observations, we proposed a system involving the continuous

58   infusion of a specially formulated nasogastric feed over a ten-day period with a

59   minimum of ten-day interval between each cycle to avoid the effects of keto-

60   adaptation. The continuous nature of the infusion, as well as the ketogenic effects

61   produced, and in contrast with bolus feeding, helps to create and maintain a sense of

62   satiety (24, 25).

63   Methods

64   Anthropometric and bio-impedance data from 629 patients who underwent KEN

65   were collected before and after completing each ten-day cycle. The study focused

66   retrospectively on the British cohort of patients undergoing a prospective multicenter

67   pilot study on Ken diet from 2006 to 2017 and were not included in previously

68   published results (14). In particular the study refers to measurements made in the

69   first three cycles of treatment. Patients who were responding but incompletely

70   treated were eligible to continue with further cycles. Exclusion criteria included

71   pregnancy, type I diabetes mellitus, severe hepatic or renal insufficiency (GFR <

72   20ml/h), inherited metabolic disorders and age < 16 years. Weight, height, waist and

73   hip circumference, as well as bio-impedance measurements were carried out

74   immediately before the beginning of a KEN cycle and ten days following the

75   completion of a KEN cycle.

76   Basal metabolic rate-weight ratio was measured at baseline and after each cycle by

77   indirect calorimetry with a coefficient of variation of <10% was used for accurate

78   analysis.

79   Patients repeated the KEN treatment cycle as many times as was required to

80   achieve their target weight based on bio-impedance data.

81   The study focuses retrospectively on the change in outcomes from the first cycle to

82   the second cycle and from the first cycle to the third cycle.

83   Informed consent was obtained from all individual participants included in the study

84   and this have been performed in accordance with the ethical standards as laid down

85   in the 1964 Declaration of Helsinki and its later amendments or comparable ethical

86   standards. Ethical approval was obtained from the University of Rome La Sapienza

87   Ethics Committee, patients were self-referred and stratified for age and gender.

88   The following outcomes were explored: waist circumference, BMI, fat mass, lean

89   mass, dry lean mass, phase angle, wellness marker, water mass as a percentage of

90   total body weight. The cycle 1, 2 and 3 outcomes were analyzed using descriptive

91   statistics (either mean and standard deviation, or median and inter-quartile range

92   depending on the data distribution) summarizing the outcome at each cycle.

93   Statistical tests were used to test for significant differences between paired cycle 1

94   and cycle 2 outcomes and also between paired cycle 1 and cycle 3 outcomes.

95   Where changes in outcomes between timepoints were found to be normally

96   distributed, the paired t-test was used, whereas where the changes in outcomes had

97   skeweddistributions, the Wilcoxon signed-rank test was used.

98   Linear regression was used to examine associations between changes in both

99   phase angle and BMR/weight with percentage weight change Initially the simple

100   relationship between variables was examined, and subsequently multiple linear

101   regression was used to re-examine the relationships after adjusting for two pre-

102   specified confounding variables.

103   A six-French polyurethane nasogastric tube (Pennine, UK) was placed by a trained

104   nurse or physician. In addition, patients received a medication pack, which included,

105   multivitamins and polyethylene glycol-based laxatives to ensure daily bowel

106   movements. Patients were provided with Ketostix™ (Bayer, Switzerland) for daily

107   urinalysis to assess for evidence of ketonuria. Patients were asked to provide a daily

108   record of their weight, ketonuria, hunger assessment (subjective scale of 1 to 10),

109   and bowel movements for the duration of the ten-day cycle. Ketonuria was used as

110   indirect indicator of ketonemia and was collected for observational reasons only.   At

111   the end of the KEN cycle, patients attended the clinic for removal of their nasogastric

112   tubes and repeat anthropometric and bio-impedance measurements. Patients were

113   asked to adhere to a low-carbohydrate unsupervised diet and attended ten days later

114   for further anthropometric and bio-impedance measurements. The K1000™

115   (Nutrimed 2000, Ancona, Italy) formula provides 65g daily protein (providing 1.2g/kg

116   ideal body weight) in an electrolyte-rich solution. Carbohydrate and fat intake was

117   completely restricted for the duration of the cycle.

118 Four-lead bio-impedance analysis measuring impedance at 5 and 50kHz, resistance

119 at 50kHz, reactance and phase angle at 50kHz were carried out using the Bodystat™

120 1500MDD analyzer (Bodystat, Isle of Man) (30-31).

121 Results

122 Results were available for the 50 days encompassing 3 treatment cycles in 629

123 patients. The results produced clinically relevant changes for all analyzed

124 parameters (Tab.1 and 2).

125 PAUL: could you test collectively (by using ANOVA) differences in cyles 1, 2 and 3?

126 There were significant decreases in weight, waist circumference, BMI, fat mass, lean

127 mass, dry lean mass and phase angle. Quantitative changes in lean mass and dry

128 lean mass were negligible with respect to changes in fat mass. There was also a

129 statistically significant increase in water mass as a percentage of total body weight

130 and "wellness marker" from cycle 1 to cycle 3.

131 There was a significant negative association between change in BMR/weight from

132 cycle 1 to cycle 2 and percentage change in weight during the same period.

133 However, this association was no longer significant after adjusting for changes in

134 waist circumference and fat mass.Change in fat phase angle from cycle 1 to cycle 2

135 was not associated with percentage weight change

136 **PAUL:** Diffence in study outcome in age,-sex or BMI in stratified groups ?

137 Overweight vs obese (people with BMI >30)

138 When considering the change from cycle 1 to cycle 3, there was a significant

139 association between change in BMR/weight and change in weight, which remained

140 significant after adjusting for changes in phase angle, fat mass and waist

141 circumference. A one-unit increase in BMR/weight was associated with a 2.4%

142 reduction in weight. There was no significant association between change in phase

143 angle from cycle 1 to cycle 3 in the simple analysis. However, after adjustments

144 greater change in phase angle was associated with a greater weight loss.

145 PAUL : Univariate linera regression analysis should also be performed for other

146 counfonsing factors among all variables tested. Associated variables should then be

147 included in adjustments models.

148 PAUL: Can cycle 3 be also be tested/included ?

149 Most patients' daily activities were not restricted, but many chose to spend their

150 period of treatment away from the workplace. By the fifth day of treatment, 24% of

151 patients reported a strong sense of asthenia, despite normal blood pressure levels.

152 Twelve percent of patients reported a mild sense of hunger (score 2-4 / 10). Twenty-

153 two percent of patients (n=138) were known to have type II diabetes mellitus

154 receiving treatment for their condition, 92% (n=127) of these patients under KEN

155 infusion were able to suspend their medication without adverse effect on their

156 glucose homeostasis. No cases of clinically significant hypoglycemia were reported.

157 Similarly, 80% of patients on anti-hypertensive medication also were able to suspend

158 their medication during KEN infusion. Tube displacement and blockage occurred in

159 3% of cases but did not interrupt completion of the treatment. Patients with mild renal

160 impairment or on anticoagulant therapy underwent close laboratory monitoring

161 during treatment and completed KEN treatment successfully without adverse effects.

162 One patient with renal salt wasting required supplemental sodium chloride to

163 maintain electrolyte stability. Patients on Warfarin therapy were able to halve the

164 dose for the duration of KEN treatment, whilst maintaining adequate anticoagulation.

165 Following KEN treatment, patients gained an average of 0.8kg after each of the ten-
166 day intervals.

167 Discussion

168

169

170

171 This study was undertaken to investigate the hypothesis that KEN treatment results
172 in selective fat loss and to assess patient safety and tolerability. Historical controls
173 would suggest intensive dietetic intervention can achieve 1-2% weight reduction over
174 a period of ten days. This modified fast provides a total of 205 – 270 calories and the
175 6kg net weight loss observed in ten days is of the same order of magnitude as
176 observed following dietetic interventions in healthy and obese individuals over one
177 year (32).

178 It might be assumed that such rapid weight loss was the consequence of relative
179 dehydration, but the hallmark of successful KEN treatment is the phenomenon of
180 selective fat loss without detriment to dry lean mass.

181 This effect might be due to the reduction in lipogenesis and increased lipolysis (33,
182 34).

183 Nair et al. reported that beta-hydroxybutyrate decreases leucine oxidation and
184 promotes protein synthesis in human (35).

185 An other mechanism implicated in preservation of lean mass may be due to interaction
186 of branched-chain amino acid leucine with the insulin signaling pathway to stimulate

187 downstream control of protein synthesis, resulting in maintenance of muscle mass

188 during periods of restricted energy intake but high protein intake (36).

189 When water mass was expressed as a percentage of body weight in our patients,

190 there was indeed an observed 1-2% increase after KEN therapy.

191 The study explored regression analysis of the outcomes percent change in weight from

192 cycle 1 to cycle 2 for the predictors Phase angle and BMR / Weight. BMR/Weight

193 showed a statistically significant correlation with percent change in weight in univariate

194 analysis and multivariate analysis. Phase angle failed as predictor of weight loss in

195 Ken in multivariate analysis. A proportion of 3:1 increase was reported for BMR/

196 Weight compared to percent change in weight in multivariate analysis. This stand to

197 conclusions that metabolically active lean body tissue increased on a 1:3 basis against

198 percent weight loss after each Ken cycle.

199 KEN treatment was well tolerated and the few mild to moderate adverse effects

200 reported were all classified as reversible (Tab 4). Despite the placement of a fine-bore

201 nasogastric feeding tube, KEN treatment may be considered a relatively non-invasive

202 technique, when compared to weight management strategies such as endoscopic

203 placement of intragastric balloons, endoscopic restrictive procedures and bariatric

204 surgery. Tube-related complications, which included tube displacement and occlusion,

205 were rare and did not lead to treatment failure.

206 It has been proposed that the mechanism of action of KEN treatment in inducing

207 continuous satiety is two-fold: the continuous infusion of protein and electrolyte-rich

208 solution into the small intestine producing continuous release of the satiety hormone

209 Peptide YY, and the effects of ketogenic metabolism in suppressing hunger (33).

210   Effects of keton bodies (KBs) on appetite might be explained by the reduction in

211   appetite control hormones, as ghrelin and leptin (16).

212   Preliminary data on mice suggest a third mechanism based on KEN-related delayed

213   colonic transit and a subsequent increase in butyrate concentrations as a result of

214   bacterial fermentation, as this may increase insulin sensitivity. Stimulation of sweet

215   taste receptors on the tongue have also been shown to stimulate the release of

216   insulin, counteracting the effects of ketogenesis (35).

217   We would like to highlight that ketosis is a physiological mechanism described by the

218   biochemist Hans Krebs to differentiate it from the pathological keto acidosis seen in

219   type 1 diabetes. In physiological ketosis ketonemia reaches maximum levels of 7/8

220   mmol/l (it does not go higher because the central nervous system is able to use KBs

221   efficiently for energy in place of glucose) (16)

222   However, the majority of recent studies seem instead to amply demonstrate that the

223   reduction of carbohydrates to levels that induce physiological ketosis can lead to

224   significant benefits in blood lipid profile (16)

225   In summary, individuals with obesity, metabolic syndrome, insulin resistance and type

226   2 diabetes are likely to see symptomatic as well as objective biochemical

227   improvements on very low- carbohydrate diet. Glucose control improves not only

228   because there is less glucose coming in, but also because systemic insulin sensitivity

229   improves as well.

230   Current studies are on-going to demonstrate the long-term sustainability of KEN

231   treatment, which will clearly depend on the lifestyle changes adopted by patients

232   after completing KEN therapy. Preliminary data suggest (14) 85% sustainability at

233   one year, i.e. patients regain a mean of 15% of their pre-treatment weight at one

234   year following completion of the required number of KEN treatment cycles. A ten-fold

235   reduction in all-cause mortality following KEN treatment has been observed (14).

236   New strategies are being developed to assist patients in maintaining their rate of

237   weight reduction between KEN treatment cycles (36,37).

238   KEN treatment is safe, well tolerated and results in rapid fat loss without detriment to

239   dry lean mass. Controlled prospective research studies are warranted to compare

240   KEN treatment with other more balanced dietary interventions.

244   Author Contribution Statement: CP, RS, AF conceived the study; RS and VL

245   collected data, PB analyzed data. CP, RS, AF, GC, VL, wrote the paper, CP had

246   primary responsibility for final content. All authors red and approved the final

247   manuscript.

248   Conflict of interests

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Table 1: Comparisons of changes in outcome from Cycle 1 to Cycle 2

Outcome	n	Cycle 1	Cycle 2	Change Cycle 1 to 2 (95% CI)	P-value
Weight	228	92.6 [80.6, 111.0]	89.3 [77.5, 107.4]	-3.7 [-4.2, -3.2]	<0.0001#
Waist circumference	227	104 [93, 115]	100 [90, 112]	-3 [-4, -3]	<0.0001#
BMI	226	33.6 [29.8, 37.8]	32.4 [28.9, 37.0]	-1.3 [-1.5, -1.1]	<0.0001#
Fat mass	226	38.4 [29.1, 46.3]	34.6 [27.5, 42.6]	-2.8 [-3.1, -2.4]	<0.0001#
Lean mass	223	52.9 [47.5, 65.2]	52.3 [46.9, 63.6]	-0.8 [-1.1, -0.5]	<0.0001#
Phase angle	223	5.91 ± 0.78	5.89 ± 0.90	-0.02 (-0.09, 0.05)	0.58*
Wellness marker	211	0.875 ± 0.022	0.876 ± 0.022	0.001 (-0.001, 0.003)	0.32*
Dry lean mass	225	15.1 ± 4.2	14.9 ± 4.1	-0.1 (-0.2, -0.1)	<0.0001*
Water mass as a % of total body weight	223	43.7 ± 5.2	44.6 ± 5.7	1.0 (0.7, 1.2)	<0.0001*

Statistics are: mean ± standard deviation plus mean change (95% confidence interval), or median [inter-quartile range] plus median change [95% confidence interval]

P-value from Wilcoxon Signed-ranks test; * P-value from Paired t-test; ~ descriptive statistics presented on the patients with both Cycle 1 and Cycle 2 outcomes available

Table 2: Comparisons of changes in outcome from Cycle 1 to Cycle 3

Outcome	n	Cycle 1	Cycle 3	Change Cycle 1 to 3 (95% CI)	P-value
Weight	126	95.9 [82.8, 115.7]	89.6 [78.4, 108.9]	-6.4 [-7.3, -5.6]	<0.0001#
Waist circumference	125	107 [97, 118]	101 [91, 112]	-6 [-8, -5]	<0.0001#
BMI	124	34.7 [31.2, 38.7]	32.8 [29.0, 36.2]	-2.4 [-2.8, -2.0]	<0.0001#
Fat mass	124	39.4 [32.1, 46.3]	34.3 [27.2, 41.8]	-4.9 [-5.8, -4.1]	<0.0001#
Lean mass	124	54.1 [47.5, 69.1]	52.4 [46.6, 67.8]	-1.3 [-1.6, -0.8]	<0.0001#
Phase angle	123	5.91 ± 0.87	5.77 ± 0.90	-0.13 (-0.21, -0.05)	0.002*
Wellness marker	117	0.875 ± 0.022	0.878 ± 0.022	0.003 (0.001, 0.006)	0.02*
Dry lean mass	124	15.1 ± 4.2	14.9 ± 4.1	-0.2 (-0.3, -0.1)	0.0002*
Water mass as a % of total body weight	124	43.1 ± 4.9	44.7 ± 5.9	1.6 (0.8, 2.4)	0.0001*

Statistics are: mean ± standard deviation plus mean change (95% confidence interval), or median [inter-quartile range] plus median change [95% confidence interval]

P-value from Wilcoxon Signed-ranks test; * P-value from Paired t-test; ~ descriptive statistics presented on the patients with both Cycle 1 and Cycle 2 outcomes available

Table 3: Linear regression analysis examining how changes in study meaures were associated with percent change in weight

Predictor	Unadjusted linear regression			Adjusted linear regression (*)		
	n	Regression coefficient	p-value	n	Regression coefficient	p-value

		(95% CI)			(95% CI)	
Cycle 1 to 2 Change in phase angle	223	0.12 (-0.77, 1.01)	0.79	222	0.22 (-0.39, 0.83)	0.47
Change in BMR / weight	222	-3.33 (-4.04, -2.61)	<0.0001	222	0.37 (-0.54, -1.29)	0.42
Cycle 1 to 3 Change in phase angle	123	0.67 (-1.18, 2.53)	0.47	121	-1.34 (-2.27, -0.40)	0.006
Change in BMR / weight	124	-3.99 (-4.68, -3.29)	<0.0001	121	-2.38 (-3.28, -1.47)	<0.0001

(*) Adjusted for change in waist circumference, change in fat mass, in addition to change in phase angle, change in BMR/weight

Table 4 Complications/Side effects

Number of patients	Complications/Side effects
2	Diarrhoea
4	Panic attack
54	Asthenia
1	Paroxysmal Tachycardia
3	Difficult NG intubation
1	Hyponatremia (patient with diabetes insipidus)
10	Pharyngeal irritation
1	Hypertension
6	Tube dislocation without further complications