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A Designer Sugar, Karbolyn®, Leads to Tighter Sugar Control than Glucose in a Pre-Diabetic Cohort

Jeff Golini, Ian C. Clift, Muhammad M. Qureshi, and * Wendy L. Jones

Royal Knight Incorporated, Rochester Minnesota, USA

Abstract

Aim: KarboLyn®, a designer sugar for elite athletes, provides a rapidly metabolized carbohydrate to the muscle, without the 'crash'. Recent investigations have suggested that KarboLyn® may be differentially processed by those with impaired glucose control. Therefore, the aim of the study was to determine whether KarboLyn® can promote a more controlled glucose utilization pattern for individuals with insulin resistance.

Materials and methods: KarboLyn® is tested alongside glucose in controls, pre-diabetics, and Type 2 (non-insulin dependent) diabetics involved in light exercise to assess the differences in blood glucose patterns. Individuals had their baseline glucose drawn before consuming the KarboLyn® or a glucose drink. Each participant then walked slowly on a treadmill until it was time for a blood draw, according to the protocol. The study lasted two hours.

Results: After spiking with glucose, the pre-diabetic's blood glucose readings displayed a downward trend resembling a series of extended plateaus rather than a sweeping curve indicative of the body's inability to maintain tight control over its blood glucose level. The KarboLyn® volunteer's spiking and downward pattern resembled the curve from the normal KarboLyn® user's data. Notable differences in the Type 2 diabetic volunteer's response were observed in some individuals provided KarboLyn® (at 10 grams) when compared to glucose.

Conclusions: Changes in glucose metabolism occurred during KarboLyn® ingestion versus glucose ingestion. Most notably are a slower peak glucose reading in all groups' tests and a more rapid return to baseline in the normal, pre-diabetic, and some individuals in the Type 2 diabetic, groups.

Trial registration: ISRCTN - 58611690 (completed 22/11/2016) 'Retrospectively registered'

Keywords: Karbolyn®, type 2 non-insulin dependent diabetics, pre-diabetic.

* Corresponding author: Royal Knight Incorporated, Rochester Minnesota, USA.

Introduction

With obesity on the rise, affecting 13% of the population globally, and a well-known risk factor for insulin resistance and T2D (Morigny *et al*., 2015), Menke *et al*., 2015), new glucose utilization strategies are desperately needed for athletes/ non-athletes with metabolic variation. In the US, 70% of the population is overweight and 31% are considered obese (Tamashiro *et al*., 2011), many also falling into the pre-diabetic and diabetic populations that could benefit from alternative forms of sugar delivery during exercise. Hyperglycemia, which results from a defective utilization of diet-derived glucose through changes in insulin sensitivity and production (Ramasarma and Rafi, 2016), might be modulated via ingestion of modified sugar products that reduce the proportion of glucose delivered to the blood stream.

Originally developed as a designer sugar for athletes interested in carbohydrate loading, KarboLyn®, considered a nutritional supplement as defined under the Dietary Supplement Health and Education Act (DSHEA) of 1994, was designed by All American® Pharmaceutical to provide both a rapidly and effectively metabolized carbohydrate to the muscle, without the 'crash' that often accompanies these energy bursts. From initial exanimations, it was also speculated that KarboLyn® may promote a more controlled utilization pattern for individuals with specific types of insulin resistance.

It has been documented that maintenance of glycemic levels, through diet, exercise, and even surgical resection of the stomach (Inge *et al*., 2016), may reduce the risk of micro vascular disease and other health risks over time (Nathan, D.M., 2015). Below, glucose and KarboLyn® are tested in similar populations to determine if delivery of a polysaccharide compound can lead to reduced glucose peaks and a more rapid return to baseline blood glucose levels during exercise, thus adding in tighter glycemic control.

The Aim of the Study

Is a focus on comparing blood glucose availability during 120 minutes of light exercise after ingestion of either glucose or the proprietary homopolysaccharide compound KarboLyn®. It sought to document two things, (1) whether or not KarboLyn®, a homopolysaccharide compound consisting of 'B' and 'A' type starch complexes, had a more moderate impact on blood sugar levels in normal individuals during light aerobic activity, and, (2) observe the effect KarboLyn® had on pre-diabetic individuals, i.e. whether or not they would show the same controlled glucose utilization curve, as normal individuals, with this product. The product was also tested in a small cohort of T2D with mixed results suggestive of variations in response profiles for diabetics taking KarboLyn®.

Materials and Methods

The Product

KarboLyn® is a proprietary ratio of potato, corn and rice starches a modified combination of homopolysaccharides that are absorbed rapidly with a more sustained release of glucose over time. The glycemic Index (GI) for KarboLyn® has been rated between 80 and 100. Above 60, foods are considered able to elevate blood glucose rapidly and to a greater degree.

The Placebo

Common table sugar, glucose, which is the reference standard for glycemic index, set at the maximum value of 100 mg/dL.

All Volunteers

Everyone observed a minimum of an 8-hour fast. After this, they were randomized to receive either KarboLyn® (50 grams) or the placebo, glucose (50 grams). They were then asked to walk on a treadmill (~1mph) for a period of 2 hours. Subjects were asked to stop and sit down for blood samples to be drawn. Blood samples were drawn at '0' (before consumption), and at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, and 120 minutes, similar to other glucose utilization studies (Oshakbayev *et al*. 2017) unless otherwise noted.

Normal Controls

A total of 24 people were recruited from the Missoula Montana area. To qualify, the individual was required to have an 8 hour fasting blood glucose level of under 100 mg/dl.

Pre-Diabetics

A total of 12 people (medically confirmed pre-diabetic) were recruited from the Missoula Montana area.

Diabetics

Two trials were conducted. In the 50 gram trial, A total of 12 T2D volunteers from the Missoula Montana area were enrolled, based on two criteria, 1. A medical diagnosis of T2D diabetes, and 2. A prescription for an oral medication for glucose control.

A subsequent study utilizing 10 grams of KarboLyn® or glucose was conducted, one week apart, on six subjects with documented diabetes. For the 10 gram trial: 6 volunteers were used and tested 1 week apart with KarboLyn® on the first week and glucose the second week. All other conditions were the same.

Statistics

A two-sample t-test was used to compare the results of each time point between the KarboLyn® treated and glucose treated groups in the 50 gram trials. During the 10 gram diabetic trial, KarboLyn® and glucose were administered sequentially, one week apart on the same individual. A

matched pair analysis (paired t-test) was used to describe differences for these individuals.

Results

Volunteers showed a distinct, proportionally rapid rise in glucose levels, spiking at 30 minutes for both KarboLyn® and the glucose placebo in normal controls. Both also showed a rapid downward trend for the first 15 minutes post peak, continuing at a lesser incline until about 75 minutes (Fig 1A). Normal individuals seemed to have a reduced spike from glucose, than from KarboLyn®, as noted in the maximum average blood glucose reading of 107 mg/dL for the KarobLyn® group and 100 mg/dL for the control group. This increase was mitigated to within 2 mgs (19 and 17, respectively) when both groups were adjusted against their baseline values. Without exception, both groups ended with a lower blood sugar numbers than their starting values. However, when adjusted to baseline, normal individuals seemed to metabolize KarboLyn® at a faster rate, with blood glucose dipping below baseline at 60 minutes versus 90 minutes for the glucose control (Fig 1b).

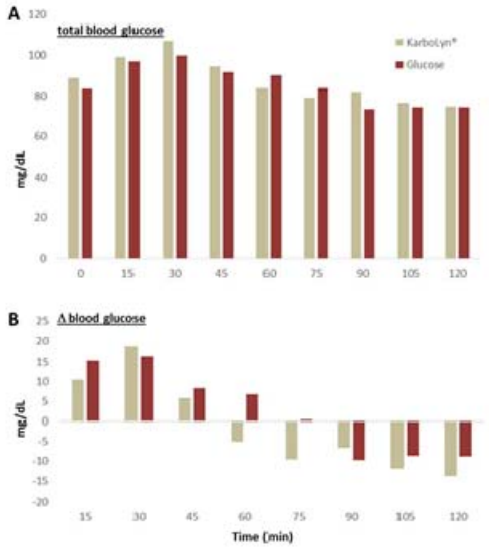

Figure 1: Blood glucose change in a control cohort

The pre-diabetic group showed distinct disproportional patterns of rise and fall between the KarboLyn® and glucose participants. Both groups showed a rapid rise in blood glucose levels, but each group behaved completely different in their spiking and downward trends. The glucose group spiked between 15 minutes and 30 minutes. The downward trend resembled a series of extended plateaus rather than a sweeping curve indicative of the body's inability to maintain tight control over its blood glucose level. Blood sugar returned to a normal level between 75 - 90 minutes and remained there (Fig 2a-b). The KarboLyn® volunteer's spiking and downward pattern resembled the curve from the normal, non-diabetic KarboLyn® user's data. Blood glucose spiked at 30 minutes and gave a more controlled, lower spike than the glucose group during the same period. This suggested that KarboLyn® may be utilized differently (than simple glucose) in individuals who are trending toward T2D. Their downward trend was a smooth decline with all participants' blood sugar returning to the normal range at 60 minutes and remaining there for the remainder of the study (Fig 2a), this is clarified in the baseline adjusted plot seen in Fig 2b. Between 60 minutes and 120 minutes, pre-diabetics in the KarboLyn® group maintained a lower and more consistent final blood sugar level than the glucose group. When adjusted to the average baseline values, the KarboLyn® group saw a drop below baseline at 60 minutes (-3 mg/dL), while the glucose control group only dipped below baseline at 75 minutes (-2 mg/dL) (Fig 2b). This was similar to the findings for the normal population trial.

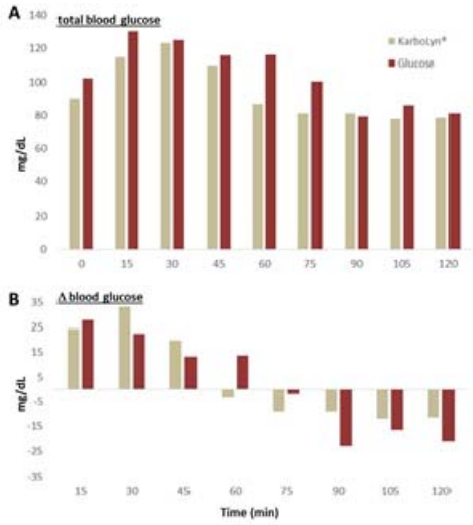

Figure 2: Blood glucose change in a pre-diabetic cohort

Diabetics did not response effectively to the 50 gram dosage of KarboLyn® or glucose within the timeframe of the study (see Table 3). Both groups failed to return to baseline by 120 minutes, which was the cut-off for the study. Noticeably, the peak for glucose was much faster than the KarboLyn® treated group. Specifically, the glucose treated rose to a peak of 235 mg/dL at 60 minutes after ingestion, whereas the KarboLyn® group reached a high of 224 mg/dL at 45 minutes. This accounted for a rise over baseline of 88 mg/dL for the glucose group and 90 mg/dL over baseline for the KarboLyn® group (Fig 3).

Table 3: Diabetic cohort (50 gram)

karbolyn® study-diabetic participant's blood glucose level (karboyln® 50 grams)									
	'0' time	15 min	30 min	45 min	60 min	75 min	-ND-	-ND-	120 min
1	153	235	243	248	237	218	***	***	138
2	123	192	218	253	250	219	***	***	162
3	151	196	220	258	266	258	***	***	190
4	161	158	171	187	188	191	***	***	147
5	195	283	289	310	329	352	***	***	306
6	88	92	109	120	140	163	***	***	93
karbolyn® study-diabetic participant's blood glucose level (glucose 50 grams)									
	'0' time	15 min	30 min	45 min	60 min	75 min	-ND-	-ND-	120 min
1	184	226	250	259	255	210	***	***	143
2	145	207	233	233	207	193	***	***	172
3	103	135	138	146	121	77	***	***	81
4	126	192	222	223	241	244	***	***	153
5	116	187	251	286	224	196	***	***	140
6	141	176	196	207	262	227	***	***	164

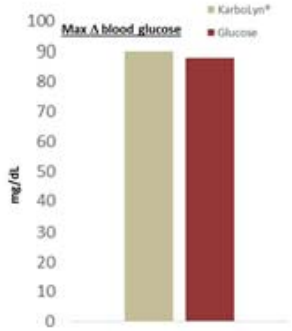

Figure 3: Peak blood glucose change in diabetic cohort receiving 50 gram dose

When the concentration of KarboLyn® or glucose was lowered in a subsequent trial to 10 grams, the peak glucose reading was much quicker, occurring at 15 minutes for the glucose treatment and 30 minutes for the KarboLyn® treatment (Fig 4a). When increases over baseline were pooled by treatment, only the 15 minute time point was significantly different (p-value=0.03), with KarboLyn® treated individual at much lower blood glucose readings, an average of 8 mg/dL versus 23 mg/dL for glucose. The peak average rise over baseline for all participants was 23 mg/dL (15 min.) in the glucose treated group and 18 mg/dL (30 min.) in the KarboLyn® treated group (Fig 4b). Notably, the reduction in blood glucose levels below baseline was increased in the KarboLyn® treated group. In the KarboLyn® group a drop to baseline occurs at 60 minutes and is consistently lower than the glucose levels until the final reading which is -22 mg/dL below baseline for KarboLyn® and -14 mg/dL below baseline for glucose.

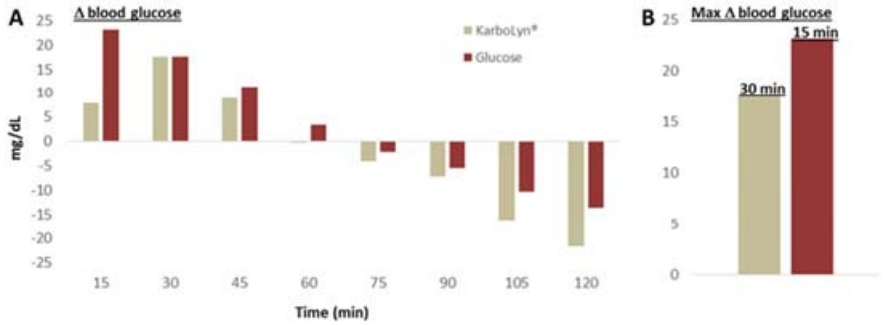

Figure 4: Maximum blood glucose change in diabetic cohort (10 gram)

Notable differences in response were observed in some individuals provided the KarboLyn® product (at 10 grams) when compared to glucose. Subjects, 1, 5, and 6 saw their blood glucose levels drop below 100 mg/dL at 120 minutes (Table 4) with KarboLyn® delivery. By contrast only one participant, subject 2, dropped below 100 mg/dL in the glucose treated group. An example responder and non-responder are represented in Figure 5. When stratified by KarboLyn® response status the average blood glucose of 'responders' was 96 mg/dL while 'non-responders' averaged 129 mg/dL at 120 minutes (Fig 5c). Despite the difference in final blood glucose, values did not reach a statistically significant difference (p=0.12).

Karbolyn® Study – Diabetic Participant's Blood Glucose Level**(Karbolyn® 10 grams)**

	'0' time	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	113	119	113	104	103	98	90	91	93
2	130	126	139	123	93	94	101	100	106
3	151	157	167	157	141	133	130	125	120
4	170	197	193	188	178	174	170	163	162
5	102	91	95	95	104	110	107	102	98
6	141	164	206	194	187	174	166	129	98

Karbolyn® Study – Diabetic Participant's Blood Glucose Level (**Glucose 10 grams**)

	'0' time	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	118	131	138	135	125	118	116	112	108
2	128	148	132	119	110	103	99	100	98
3	145	156	150	143	129	126	124	120	118
4	133	167	152	139	127	119	119	111	108
5	100	100	112	119	120	114	114	110	110
6	159	220	205	196	193	190	179	169	160

Figure 5: KarboLyn® 'Responder' and 'Non-responder' blood glucose profiles

Discussion

It is now recognized that post-prandial hyperglycemia is a risk factor for long term vascular complications associated with metabolic syndrome and disease. While Metformin, the first-line oral biguanide prescribed for diabetic management of glucose, has shown moderate efficacy in reducing blood glucose over placebo (Gadde *et al.* 2017, Rojas and Gones, 2013), post-prandial levels of glucose may be much harder to normalize than fasting glucose readings (Brod *et al.*, 2016). Reports have shown that even a marginal increase in blood glucose levels in non-diabetics was a risk factor for cardiovascular events (Balkau *et al.* (1998). Furthermore, the risk for cardiac events more than doubles within diabetic individuals during their lifetime (Rojas and Gomes, 2013), due primarily to higher blood glucose levels over time. In this study both a slower increase in blood glucose levels as well as a more rapid decline in blood glucose were observed with the KarboLyn® groups. If this pattern could be shown to continue, long term usage during exercise, by pre-diabetic and diabetic

individuals, might be beneficial in reducing cardiac risk. Though normal volunteers were able to maintain tight control over their blood sugar, a subtle improvement was noted in the timing of glucose declines in KarboLyn® users (Table 1, Fig 1b), these early declines in glucose levels below starting baseline were also noted in the pre-diabetics and low dose diabetic participants.

Table 1: Control Cohort

karbolyn® study-normal participant's blood level (karboyln® 50 grams)									
	'0' time	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	85	81	94	97	107	97	77	81	74
2	86	97	111	90	73	67	79	62	70
3	92	84	84	88	76	87	90	85	84
4	85	107	97	82	56	60	81	75	69
5	80	122	140	122	94	78	82	74	76
6	89	102	101	83	79	78	80	72	76
7	84	106	95	82	85	90	91	83	86
8	84	70	103	79	69	74	87	72	69
9	87	79	103	70	55	55	64	73	65
10	92	107	107	108	96	84	74	67	67
11	103	123	1047	93	85	74	75	83	92
12	97	112	145	140	128	106	104	94	71
Karbolyn® study-normal participant's blood glcose level (glucose 50 grams)									
	'0' time	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	57	91	88	60	85	63	47	83	75
2	104	117	117	91	87	92	91	88	89
3	98	128	139	110	97	75	75	78	77
4	91	102	82	80	83	96	67	63	74
5	79	83	92	87	79	69	52	64	62
6	91	105	93	111	101	99	98	98	88
7	81	65	60	73	79	77	88	87	85
8	77	95	78	74	78	81	81	77	78
9	56	72	80	74	85	85	61	53	67
10	80	105	97	85	70	61	55	55	57
11	86	105	116	109	101	87	79	69	57
12	99	**	155	145	135	119	88	80	84

KarboLyn® functions in a similar fashion to other complex sugar substances studied in human clinical trials (Agrawal *et al*., 2007, Yamada *et al*., 2005, Lightowler and Henry, 2009, Skrabanja *et al*., 2001). This is directly related to the types of starches (polysaccharides) contained within the food product, specifically the amount and composition of A and B type starches (Lee *et al*., 2013).

For example, shifts in blood glucose peaking was seen in response to mashed potato starch compared to glucose as well as drops below baseline (Lightowler and Henry, 2009). In another study conducted in Type 1 diabetes, substituting half of the starch in a meal, led to a quicker rise in glucose, consistent with the current findings. Inconsistent, was the rapid decline in glucose load noted in the KarboLyn® group, which may be indicative of a distinct response. This response is possibly similar to the glucose suppressing effects specific to certain food products, such as rice albumin, which has been shown to decease blood glucose and plasma insulin levels (Ina *et al*. 2016).

While the mechanism of action was not investigated here, the two groups of pre-diabetic volunteers generated very different results, similar to previous findings. KarboLyn® appears to be digested and /or utilized in a different manner than simple glucose, as evidenced by the lower and slower spike in blood sugar and the controlled decline resembling a normal glucose pattern. Similar to the normal controls, a slower climb and more rapid drop off was noted in blood sugar levels of the KarboLyn® group (Fig 2, Table 2).

Table 2: Pre-diabetic cohort

Karbolyn® study-pre-diabetic participant's blood glucose level (karbolyn® 50 grams)									
	'0' time	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	92	128	157	129	110	85	69	67	75
2	82	102	76	84	57	64	70	68	73
3	84	99	99	77	70	77	84	85	88
4	85	102	113	117	102	95	92	92	90
5	99	107	130	138	106	82	65	68	75
6	99	150	164	115	77	84	107	89	71
Karbolyn® study-pre-diabetic participant's blood glucose level (glucose 50 grams)									
	'0' time	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	108	108	89	75	86	96	88	66	63
2	120	127	107	145	134	86	59	69	81
3	89	94	104	87	87	85	75	78	84
4	100	182	175	101	108	99	53	120	101
5	101	137	125	124	105	80	65	75	77
6	97	133	150	163	177	158	137	108	83

One can also speculate that with a slower climb in blood glucose followed by a sharper drop (Fig 1, Fig 2, Fig 4), KarboLyn® may be administered in such a way as to maintain a consistent (lower) blood glucose level during exercise. Additionally, certain foods that lead to slower glucose spiking have been shown to reduce long term fat deposition and increase insulin sensitivity in rats (Takeda *et al*., 2005). At high doses, while blood glucose peaks were similar between KarboLyn® and glucose treated diabetics, a slower rise to peak in the KarboLyn® group was noted, similar to what had been noted in the normal controls and pre-diabetic groups. A second trial was conducted to examine the role of KarboLyn® and glucose on the same individual using a much lower dose, 10 grams. Despite a small sample and variation in individual responses, some individuals responded favorably to the KarboLyn® and others responding better to the glucose. Additionally, several participants did not respond to either sugar favorably. Based on the response profile, participants, who were tested on both glucose and KarboLyn®, one week apart, were stratified according to their final glucose reading. Those that fell below 100 mg/dL at 120 minutes after KarboLyn® were placed in the '*responder*' category, while those that did not fall below 100 mg/dL were considered '*non-responders*.' Even after this reclassification, results did not reach statistical significance. Removal of a single outlier who did not fit in either classification, subject 302 (Table 4 – [#2]), which fell below 100 in the glucose group but not the KarboLyn® group, led to refined statistics at 120 minutes that approached significance (p=0.066).

Table 4: Diabetic cohort (10 grams)

Karbolyn® study-diabetic participant's blood glucose level (karbolyn® 10 grams)									
	'0' time	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	113	119	113	104	103	98	90	91	93
2	130	126	139	123	93	94	101	100	106
3	151	157	167	157	141	133	130	125	120
4	170	197	193	188	178	174	170	163	162
5	102	91	95	95	104	110	107	102	98
6	141	164	206	194	187	174	166	129	98
Karbolyn® study-diabetic participant's blood glucose level (glucose 10 grams)									
	'0' time	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	118	131	138	135	125	118	116	112	108
2	128	148	132	119	110	103	99	100	98
3	145	156	150	143	129	126	124	120	118
4	133	167	152	139	127	119	119	111	108
5	100	100	112	119	120	114	114	110	110
6	159	220	205	196	193	190	179	169	160

There were no statistical differences in peak glucose readings between groups within any of the four trials, suggesting a consistent delivery of glucose to the bloodstream regardless of product or metabolic status. However, it was shown that at high doses, KarboLyn® delivers a similar amount of glucose to the bloodstream but with a delay, suggesting that delivery of glucose is not impaired by the complex homopolysaccharide configuration of the product, only slowed. Peak levels of blood glucose were consistently achieved at a later time point in the KarboLyn® population, likely also due to the complex nature of the starches in the KarboLyn® product leading to slower digestion into sugar.

Conclusions

The data suggests that subtle changes in glucose metabolism occur during KarboLyn® ingestion versus

glucose ingestion. Most notably are a slower peak glucose reading in all groups tested and a more rapid return to baseline in the normal and pre-diabetic groups. Others have suggested that a slower climb is beneficial for insulin sensitivity and reducing cardiac risks due to hyperglycemia [18]. Data from the diabetic cohort was less conclusive. Although a similar blood glucose level was achievable regardless of glucose source as seen in the 50 gram dose, glucose treatment creates a quicker and more sustained blood glucose load than KarboLyn®. Nevertheless, statistical differences between treatments were not reached, though several trending statistics were notable, suggesting that a larger population pool might be necessary to reach statistical difference. Furthermore, it was observed in the 10 gram cohort, tested one week apart with either glucose or KarboLyn® that some participants responded differently to the KarboLyn® treatment than others (Fig 5). When stratified as either 'responders' – those that fell below 100 during KarboLyn® treatment, and 'non-responders' – those that did not fall below 100, even more striking differences between groups were noted. Figure 5a shows the difference in final blood glucose between 'responders' and 'non-responders.' Based on this data, a further study is planned using T2D. The questions that will be asked in this Phase '0' study are: can KarboLyn® control the rise and fall of a non-insulin dependent T2D blood sugar level in the same manner as it has shown to do in the pre-diabetics, and, can its use allow a diabetic athlete to experience all the benefits of a 'controlled spike' followed by a return of blood sugar to normal, in and of itself, without medication. However, many questions remain, including what role does initial blood glucose play in response to KarboLyn®, what factors determine KarboLyn® response, and how will participants respond over the course of several days or weeks.

Does long term KarboLyn® use lead to increased insulin sensitivity? Due to the complex nature of diabetes T2D, factors such as age of onset, years of glucose management and use of other pharmaceuticals may play a role in determining specific KarboLyn® responses. These questions can only be answered with an increased number of subjects and more detailed data collection. KarboLyn® is also currently being investigated as designer sugar for pre-diabetic athletes.

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