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**THE EFFECTS OF OMEGA-3 AND OMEGA-6
FATTY ACIDS
on
GLUCOSE TOLERANCE AND PANCREATIC
INSULIN CONCENTRATION
in
C57BL/KSJ db/db MICE**

**by
Rohini Suraj ©**

1990

Submitted to the Committee on Undergraduate Honors of Baruch College of The City University of New York in partial fulfillment of the requirements for the degree of Bachelor of Arts in Biology (Ad Hoc) with Honors.

ACKNOWLEDGMENTS

Special thanks to Dr. Ronald W. Schwizer for being my sponsor and for the use of his laboratory. His patience, encouragement and assistance was of immense help to me throughout this study.

Thanks to the Baruch College Fund for providing necessary funds, and also to Dr. Norman Fainstein, Dean, School of Liberal Arts and Sciences, who provided the money to repair a vital piece of equipment necessary for this study.

Thanks to Sean Pickering and Michael Dempsey for their assistance with laboratory work and animal care during this study.

I would also like to thank Mr. Dalchand Rampaul, Senior College Laboratory Technician, for the use of his computer and office during the preparation of this paper.

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INTRODUCTION

Diabetes mellitus is a disease that affects 5% of the population in the United States. This disease has been known to exist since at least 1500 B.C. and yet there is no cure even though billions of dollars have been spent on research toward that end (1). However, there have been major advances in the understanding and treatment of it. If current trends continue, i.e., high saturated fats consumption, one in every five Americans will ultimately become diabetic. It is the third leading cause of death, trailing behind heart disease and cancer, in the United States. The chances of becoming diabetic increase with age and excess body weight. Blindness, kidney disease, gangrene and heart disease occur at a higher rate in diabetic patients than in non-diabetics. Diabetes mellitus is thought to be a heterogeneous group of diseases rather than a single disease. This is supported by recent work in three seemingly unrelated fields: genetics, immunology and virology. It is believed that the disease is caused by an interaction between environmental factors (including dietary intake) and heredity (1).

The two types of diabetes are maturity-onset and juvenile-onset diabetes. Maturity-onset diabetes accounts for over 90% of the diabetic cases and occurs primarily in people who are over the age of 40 and obese (1). This type of diabetes is thought to be caused by a lack of proper binding between insulin and its receptors in target cells such as liver, muscle and adipose tissue. This type of diabetes tends to occur in families and it is thought to be inherited. It is also known as non-insulin-dependent diabetes mellitus. One important aspect in the treatment of maturity-onset diabetes is the regulation of a proper diet and control of body weight.

Juvenile-onset diabetes, on the other hand, occurs in less than 10% of the diabetic cases and usually in people who are under the age of 20. This type of diabetes is caused by the destruction of beta cells in the Islets of Langerhans of the pancreas, resulting in only 10% efficiency in producing insulin (1). As such there is a lack of insulin. This form of diabetes is also known as insulin-dependent diabetes mellitus. It is more lethal than maturity-onset diabetes due to rapid destruction of beta cells in the islets. Insulin therapy can control the early symptoms of the disease, but not the long term effects, such as thickening of the basement membrane in blood vessels and blindness. Therefore, more effective therapy is needed.

Previous studies have shown that diabetes mellitus is positively correlated with saturated fatty acid consumption (2). A high percentage of the diabetic population in the United States consumes high levels of saturated fats. A lower incidence of diabetes mellitus has been observed among vegetarians and Eskimos, whose dietary intake is comprised of high levels of polyunsaturated fats and low levels of saturated fats (3). Studies have shown that Greenland Eskimos and Danes eat comparable amounts of fats, but their composition varies. The Eskimos have diets containing high levels of polyunsaturated fatty acids (Omega-3) and less saturated fatty acids than the Danes, who have a higher incidence of diabetes mellitus (4). This suggests that the diet plays a significant role in the remarkable glucose tolerance in Eskimos, but heredity may also play an important role.

Fig. 1 Cyclo-oxygenase Chart



Fig. 1 MAJOR METABOLITES OF CARBOXYLIC COMPOUNDS AND LIPIDIC (FORM-5) FROM SCHEM

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Fig. 1 Major Matabolites of Linoleic (Omega-6) And Linolenic (Omega-3) Fatty Acids.

The two major classes of fatty acids are polyunsaturated and saturated fatty acids. Two types of polyunsaturated acids are linolenic (omega-3) and linoleic (omega-6) acids. The major metabolite of omega-3 is eicosapentanoic acid (EPA), whereas arachidonic acid (AA), is the major metabolite of omega-6 acids.

In the pancreatic islet, both the cyclo-oxygenase and lipoxygenase pathways are used to metabolize AA, however, as shown in fig. 1, only the lipoxygenase pathway is used to metabolize EPA (5). This is due to the fact that EPA is a poor substrate for the cyclo-oxygenase pathway. Prostaglandin E2 (PGE2), an insulin inhibitor, is a metabolite of AA when metabolized along the cyclo-oxygenase pathway (6). 12-hydroperoxyeicosatetraenoic acid (12 HPETE), an intermediate metabolite of the lipoxy-genase pathway, can be converted to 12-hydroxyeico-satetraenoic acid (12 HETE), an insulin stimulator (7). Since it is metabolized along the lipoxygenase pathway, EPA does not produce an appreciable amount of PGE3, and EPA also inhibits the formation of AA (8). Thus, the metabolism of EPA stops the production of an insulin inhibitor and increases the production of an insulin stimulator. This could be one of the significant reasons that diabetes mellitus is rare among Eskimos and vegetarians whose dietary fats are comprised mainly of omega-3 and omega-6 fatty acids, respectively.

Fatty acids in the diet can also cause changes in blood platelet phospholipid membranes (9). Polyunsaturated fatty acid components of the phospholipid membrane of Friend erythroleukemia cells decreased when the cells were grown in a mono-unsaturated medium, and increased when they were grown in a polyunsaturated medium with a major decrease in monounsaturated components (10). The membrane lipid environment influences insulin receptor binding such that the more unsaturated membranes are, the more responsive they become to insulin. 3T3-LT adipose cells exposed to unsaturated fatty acid exhibited up to an 80% increase in insulin binding and insulin-stimulated 2-deoxyglucose uptake, whereas cells exposed to mono-unsaturated fatty acids of the same chain length showed less change (11). Cells enriched in unsaturated fatty acids have an increased number of insulin receptors (10) and would thus be expected to demonstrate increased insulin sensitivity.

Among the animal models available for the study of diabetes mellitus is the C57BL/KsJ db/db mutant. Mutation of an autosomal recessive gene on chromosome 12 in this strain results in the development of diabetes. The mutation is said to cause a metabolic disturbance similar to the disturbance that occurs in maturity-onset diabetes in humans. In the db/db mice, hyperglycemia occurs after the age of 4 weeks and rises rapidly to very

high levels (e.g., 1000 mg/dl) at about 8-12 weeks of age. After this period the animals become severely diabetic, lose weight, and die before they are 10 months old (12).

Normal plasma insulin levels are present for about the first 8 days of life in db/db mice. It then increases at 10-14 days of age and continues to rise until the animals are 6-8 weeks old, after which it decreases to levels that are either below normal or are very low in relation to the magnitude of hyperglycemia (12). The insulin content of the pancreas is also decreased as a result of destruction of the insulin-producing beta cells, with transient and/or inadequate replacement (13). While studies have shown that isolated islets from diabetic mice contain lower than normal levels of insulin from 5-20 weeks of age (12), the major defect in db/db mice seems to be reduced insulin insensitivity, i.e., poor binding of insulin to its receptors. Since it has been shown that polyunsaturated fatty acids increase insulin sensitivity, the db/db mice seem to be an ideal model for this study.

Since previous studies have shown that polyunsaturated fatty acids influence insulin secretion and sensitivity, the purpose of this study was to show the effects of dietary omega-3 and omega-6 fatty acids on glucose tolerance and pancreatic insulin concentration in C57BL/KSJ db/db mice.

EXPERIMENTAL DESIGN

A total of 24 C57BL/KsJ female mice were used in this study. Twelve animals were of the db/+ (normal) genotype and 12 were of db/db (diabetic) genotype. Four animals of each genotype were separated into three groups: A (96W meal only); B (96W meal + 5% linoleic acid) and C (96W + 5% linolenic acid). To monitor the progress of diabetes mellitus, animal body weights were recorded weekly, and a plasma glucose assay was performed biweekly after overnight fasting. After 8 weeks on the diets, a 2-hour glucose tolerance test was performed, the animals were sacrificed, and the insulin content of the pancreas was determined by radioimmunoassay.

MATERIALS AND METHODS

Animals

A total of 24 female C57BL/KsJ mice (12 db/db and 12 db/+ controls) at 5 weeks of age, were obtained from the Animal Resources Department of The Jackson Laboratory (Bar Harbor, ME). The animals were housed one per cage (Nalgene propylene cages) and maintained in a 12:12 hour light:dark cycle. Thrice weekly they were fed and the cages cleaned. A fresh layer of animal bedding was supplied to each cage after cleaning. Clean water at pH 2.7 (adjusted with HC1) was supplied at the last weekly feeding, so that water was readily available at all times.

Diet Preparation and Feeding

Two types of oil-supplemented meal were prepared using 96W powdered animal meal obtained from the Emory Morse Co. Linoleic oil (60%; Sigma chemical # L-1626, lot # 68F-0042) was added to 1 kg of 96W meal for a total oil concentration of 5%. The meal was mixed for approximately 10 minutes in a food processor. Linolenic oil (55%; ICN Biochemical # 102188, lot# 24496) was used to prepare the other diet to a total of 5% oil. Food was loosely packed in ceramic cups and placed on the bottom of the cage. The cups were refilled every other day.

Body Weight Determinations

In order to monitor progression of diabetes and obesity body weights (in grams) were recorded weekly using an electronic Sartorius balance (model MP9).

Plasma Glucose Assay

Blood samples were obtained biweekly from the postorbital sinus of animals that were fasted overnight. Heparinized capillary tubes were used to obtain the samples, which were then spun in a hematocrit centrifuge (Clay Adams Autocrit II). The glucose concentration was determined using the colorimetric glucose-oxidase method (14). A glucose standard (100 mg/dl) and samples were diluted in 0.1% benzoic acid in distilled water using a digital diluter (Hamilton) for a total of 200 ul. Ten ul of plasma was used from db/+ mice and 5/ul was used from the db/db mice. Due to increased glucose concentration in the plasma of diabetic mice, the concentration obtained from the db/db mice was later multiplied by a factor of 2 to account for the different sample sizes. Three milliliters of color reagent (glucose oxidase + peroxidase) (14) was added to each sample and standard, The tubes were incubated for 45 minutes at room temperature in the dark. The contents of each tube was then read at 450nm in a colorimeter (Milton Roy Spectronic 21). The unknown concentration was read on the colorimeter after calibration using a standard glucose concentration of 100 mg/dl in 0.1% benzoic acid.

Glucose Tolerance Test

This test was carried out in the eighth week of the study on animals fasted overnight. A glucose load of 1 mg alpha-D-glucose per gram of body weight dissolved in 0.85% NaCl in distilled water was injected into the peritoneal cavity. The time of injection was set as time zero. Blood samples were drawn just before the glucose injection and at 30, 60 and 120 mins. after the glucose injection. Samples were assayed as described above.

Radioimmunoassay of Pancreatic Insulin

Pancreatic insulin concentration was measured by radioimmunoassay (15). On the last day of the study the animals were sacrificed by cervical dislocation. The major portion of the pancreas was removed surgically and weighed on an electronic analytical balance

(Mettler AE-166). The pancreas was then homogenized in 10 ml. of acid ethanol (1.5% HCl in 70% ethanol) using a Polytron homogenizer (Brinkmann). The extract was diluted 1:200 in borate buffer, pH 7, and assayed according to protocol described by Hales et al (15).

Duplicate samples of standards (0-300 uU/ul) and extracts were incubated with 100 ul of guinea pig antiserum and 100/ul of porcine [125] I-insulin for 90 minutes at room temperature. The tubes were then centrifuged at 3000 rpm for 10 minutes at 5° C using a Beckman refrigerated table top centrifuge (model TJ-6). The supernatant was decanted and the radioactivity in the pellet was counted for one minute in a 5-well gamma counter (Genesys) equipped with an automatic data analysis program. Assay performance was monitored by including two known plasma samples as unknowns.

Analyses of Data

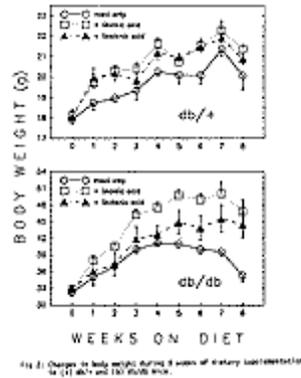
Standard deviations of the data in each group were calculated from mean values of weekly body weights, bi-weekly plasma glucose concentrations, the glucose tolerance test and insulin concentrations of the pancreas. These calculations were performed using a Sharp scientific calculator (model EL-500 II). Graphs were prepared from raw data using SigmaPlot software (Jandel Scientific).

RESULTS

Body Weights

At the beginning of the study, the 5-week-old diabetic mice (db/db) were already obese. Their mean body weight was 15 grams heavier than their db/+ controls at week zero. Both the db/db and db/+ groups gained weight after the first week, however, the db/db mice fed linoleic acid (group B) gained the most weight. Throughout the study the mean body weights were higher for groups B and C than for the mice in group A (Fig. 2a). For the db/db mice, the mean body weights of the animals in group B was higher than those in group C (Fig. 2b). The difference was significant after the third week on diet. Both the db/+ and db/db groups gained weight until the seventh week of the study (12 weeks old) after which they began to lose weight until the eighth week, when the study was terminated.

Fig. 2. Body Weight / Weeks on Diet



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 fig. 2 Changes in body weight during 8 weeks of dietary supplementation in (a) db/+ and (b) db/db mice.

Plasma Glucose

The plasma glucose levels at the start of the study, for the db/+ mice in groups A, B and C, were within the normal range (70-225mg/dl). This state of normalcy continued throughout the study even though the plasma glucose levels rose in all three groups. Allowing for standard deviation, the plasma glucose levels of all three db/+ groups were similar. However, at the eighth week of the study, the plasma glucose of the db/+ mice in group A declined sharply and it was lower than the means for the db/+ mice in groups B and C (Fig. 3a). For the db/db groups, the mean plasma glucose level at the beginning of the study started in the normal range, but after two weeks on the diets the glucose levels in all three groups were above the normal range (Fig. 3b). Throughout the eight weeks of study, the mice fed on the two fatty acid-supplemented diets had a lower mean plasma glucose level than the db/db mice fed meal alone. Statistical analyses showed no distinct differences in plasma glucose levels among the three db/db groups.

Fig. 3 - Plasma Glucose Conc. / Wks on Diet

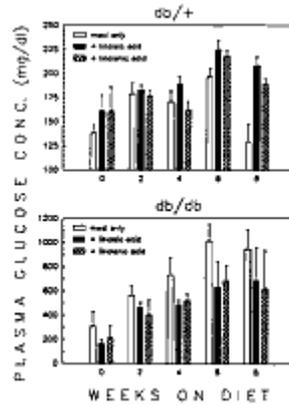


Fig. 3 Plasma glucose concentration during 8 weeks of dietary supplementation in (a) db/+ and (b) db/db mice.

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Fig. 3 Plasma glucose during 8 weeks of dietary supplementation in (a) db/+ and (b) db/db mice.

Table 1 - Pancreatic insulin chart

	96W meal	+5% linoleic acid	+5% linoleic acid
db/+	1.7±0.4	1.7±0.3	1.7±0.2
db/db	0.4±0.1	1.0±0.7	1.4±0.8

All values are means ± S.D.; unit = mU/mg wet weight.

Table 1 Pancreatic insulin concentrations following 8 weeks of dietary supplementation

Fig. 4 - immunoreactive insulin content

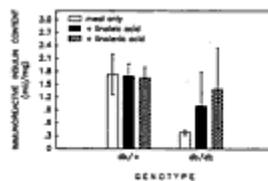


Fig. 4: Pancreatic insulin concentration after 8 weeks of dietary supplementation in db/+ and db/db mice

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Fig. 4 Pancreatic insulin concentration after 8 weeks of dietary supplementation in db/+ and db/db mice

Pancreatic Immunoreactive Insulin Concentration

After eight weeks on the diet, the mean pancreatic insulin concentration for all the normal (db/+) mice was 1.7 uU/ul. However, the mean pancreatic insulin concentration for the three groups of diabetic mice were different. The db/db mice fed meal only had the lowest mean (0.4 uU/ul), and those db/db mice that were fed 5% linolenic acid had the

highest mean pancreatic insulin concentration (1.4 uU/ul). The db/db mice that were fed 5% linoleic acid showed a pancreatic insulin level intermediate to the other two groups (Table 1). Even though there were major differences in the mean pancreatic insulin concentrations among the db/db groups, the range in each group was large enough so that the differences were not statistically significant (Fig. 4).

Glucose Tolerance Test

The db/+ mice in all three diet groups lowered their plasma glucose levels two hours after a glucose load to the level they had prior to the load. The normal mice on diet B and C had slightly higher plasma glucose levels at the start of the test than those on diet A (Fig. 5). The db/+ mice on diet C took 30 minutes longer to reach their peak glucose level than the db/+ mice on diets A and B. The diabetic (db/db) mice on diets A and B did not demonstrate a lowered glucose level even after two hours following the glucose load. However, one diabetic mouse in group B did show a return to pre-test levels after 2 hours. All mice in group C were capable of lowering their plasma glucose levels two hours after the glucose load. The peak plasma glucose concentration for the mice in group C was 900 mg/dl, whereas in group A and B it was 1100 mg/dl. The mice in Group C had the lowest plasma glucose concentration before and after the test when compared to group A and B. One mouse in this group died during the seventh week of the study. The cause of that death was unknown. Throughout the period of the study one mouse in group C had a plasma glucose concentration that was in the normal range. This mouse was obese, but probably did not have a full-fledged case of diabetes. Similar to their db/+ controls, the db/db mice in group C took 30 minutes longer to reach their peak plasma glucose level after the glucose load than did the db/db mice in the other groups.

Fig. 5 Time following Glucose injection

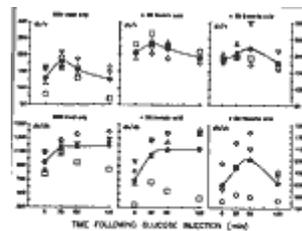


Fig. 5. The effects of 8 weeks of dietary supplementation on plasma glucose concentration during a 2-hour glucose tolerance test.

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fig. 5 The effects of 8 weeks of dietary supplementation on plasma glucose concentration during a 2-hour glucose tolerance test

DISCUSSION

The body weights were observed in order to monitor the progression of diabetes mellitus and obesity. The difference in body weights between the mice on the two fatty acid-supplemented diets and the mice that were fed on meal only was expected. This

difference is likely due to the high fat content in meals B and C relative to A, and is the reason that both groups B and C db/+ mice were heavier throughout the eight weeks of study. A similar difference was seen in the db/db mice (Fig. 2b). However, the additional difference in body weights of the diabetic mice in groups B and C cannot be accounted for. This difference may be accounted for by differences in the oils in meals B and C and/or the consumption of more food by mice in group B. This might be clarified in future studies by having pellets made from each diet and weighing the food before and after feeding.

Plasma glucose concentration was also measured in order to monitor the progression of diabetes mellitus. The reason for the sharp decline in mean plasma glucose concentration of the db/+ mice on the meal only diet in the eighth week of the study is not known. One reason could be that the mice ate all of their food just after it was placed in their cages, so that they went without food for two nights rather than one night as the other mice did. Since the amount of food consumed could not be measured using a powdered diet this cannot be substantiated. The gradual increase in plasma glucose of the db/+ mice during the eight weeks of the study could have been a result of age. The slightly higher plasma glucose concentration observed in the db/+ mice of group B and C is a result of a higher fat content in their diet. However, considering the standard deviations between the db/+ mice in all three groups, no significant differences were observed in plasma glucose concentration of db/+ mice on the three diets (Fig. 3a). The mean plasma glucose concentration of the two fatty acid-supplemented diets were lower than that of the db/db mice on diet A. This could be a result of the effects of the fatty acids on insulin levels and/or insulin binding to its receptors, thus lowering plasma glucose concentration. The latter reason is supported by a previous study (11) that polyunsaturated fatty acids increase the number of insulin receptors and thus increase binding. The rise in plasma glucose concentration above the normal range, after the first week of the study was expected. Hyperglycemia, as stated earlier, occurs after the db/db mice are 4 weeks old (12). The mice were 5 weeks old at the beginning of the study and as such it was expected that they would be hyperglycemic. These differences in plasma glucose levels however, were not significant due to the large standard deviations in all three groups (Fig. 3b). In a larger study, a greater difference in favor of the fatty acid-supplemented diets (both B and C) may be seen. This result indicates that polyunsaturated fatty acids (linoleic and linolenic acids) lower plasma glucose concentration.

After eight weeks of study, all the db/+ mice had the same mean pancreatic insulin concentrations. This suggests that the fatty acids did not have a positive or negative effect on pancreatic insulin concentration in the normal mice (Table 1 and Fig. 4). However, in the diabetic groups both fatty acids did affect pancreatic insulin concentration as shown by the higher insulin concentrations in these mice. In group C db/db mice, the mean pancreatic insulin concentration was in the normal range, followed closely by group B db/db mice which had an intermediate level of pancreatic insulin. This definitely shows that linolenic acid increases insulin secretion in the pancreas. This can be explained by following the metabolic pathway in figure 1. The major metabolite of linolenic acid is 12-HETE, which stimulates insulin secretion (7) and also blocks the formation of prostaglandins which are insulin inhibitors. Thus, in consuming a high level of linolenic

acid the db/db mice produce more insulin than the db/db mice on a regular diet. This study also shows that linoleic acid can also increase insulin production in the pancreas, but not as effectively as linolenic acid. This may be because the metabolites of linoleic acid include an insulin inhibitor PGE2 along with an insulin stimulator 12-HPAA. These two metabolites are then in competition to decrease or increase insulin secretion respectively. These conclusions may not be correct because the standard deviations in all three groups were sufficiently large that the pancreatic insulin levels can be interpreted as showing no significant differences. However, averages suggest that linolenic acid and to a lesser extent linoleic acid increase pancreatic insulin production to within the normal range. Future studies on a larger scale may be able to substantiate this claim.

The mean plasma glucose concentrations of the normal mice in all three groups were lowered after two hours during a glucose tolerance test. The mean values for the db/+ mice fed on high fat meal were higher than the mice fed meal only. This is probably the result of the high fat content of the meals fed to groups B and C. The fact that the plasma glucose levels went down after two hours indicates that the fatty acids did not interfere with the normal and expected action of insulin.

The db/db mice in groups A and B did not demonstrate lower plasma glucose levels two hours after a glucose load. This implies that there was a lack of insulin and/or decreased insulin binding to receptors such that plasma glucose levels could not be regulated. However, one mouse in group B did lower its glucose level to what it had been before the test. Linoleic acid may have been responsible for this, but because this occurred in only a single mouse, this finding cannot be considered significant. The most positive result occurred in group C db/db mice. All three mice (one died) showed lowered plasma glucose levels after two hours. The plasma glucose concentration in all the mice in group C took longer to achieve its peak than the mice in the other groups during the glucose tolerance test. It is assumed that linolenic acid had some effect on the absorption of glucose into the plasma. The only db/db mice that were able to regulate its blood glucose level were the mice in group C. The lowering of the plasma glucose concentration indicates that linolenic acid had an effect on insulin secretion and/or binding of insulin to its receptors. This is consistent with previous studies (9-11) that polyunsaturated fatty acids can influence insulin secretion and increase insulin sensitivity by changing the phospholipid membranes and thereby increasing the number of receptors.

Linolenic acid as shown in this study has the potential to lower plasma glucose and increase pancreatic insulin concentrations. It also increases glucose tolerance as seen by the result of the glucose tolerance test. Linoleic acid did have the ability to lower plasma glucose levels and to increase pancreatic insulin concentration but it was not as effective as linolenic acid. Linoleic acid also did not increase glucose tolerance.

Linolenic acid may be more effective because its major metabolite is an insulin stimulator and because it is more unsaturated than linoleic acid. As stated before, the more polyunsaturated the fatty acids are the more they can cause changes in the phospholipid membranes. These changes include an increased number of insulin receptors which then increase insulin sensitivity. Therefore, linolenic acid and to a lesser

extent linoleic acid increase insulin sensitivity in the membranes and insulin secretion in the pancreas.

For future work, a larger scale study is necessary to show that linoleic and linolenic acids can increase insulin sensitivity and insulin secretion. This study shows this but due to a small sample size the standard deviations were too large to definitively say that these fatty acids do increase insulin sensitivity and secretion. Another matter that should be considered is a glucose standard curve utilizing more glucose standards. This study used only one glucose standard and readings were taken that were above the standard used. The conversion of specialized diets into pellets should also be considered, If this is done, the amount of food consumed by the mice can be measured. This data can then explain the difference in weights between groups B and C db/db mice (Fig. 2).

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