Effect of Western-Style Diet on Blood Glucose Levels in Werner Deficient Mice

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Werner syndrome is a rare autosomal inherited genetic disease of premature aging. Patients have increased incidence of diabetes, as well as cancer and cardiovascular diseases. It is estimated that up to 10 million Americans may be carriers of the Werner gene mutation, which might predispose them to susceptibility for developing diabetes and other chronic diseases of aging. Western-style diets high in fat and sugar have been associated with an increase in diabetes in the general population. In order to determine if this type of dietary environment might adversely affect blood glucose levels in association with Werner gene mutations, Werner (Wrn) deficient mice were fed the ''Surwit'' diet, comprising 35.5% lard, 32.7% table sugar, and 20% protein. Body weights and blood glucose levels were measured. All mice had a significant increase in body weight after 12 days of being fed the Surwit diet compared to mice fed the regular rodent chow. Similarly, all mice had a significant increase in blood glucose levels after 12 days of being fed the Surwit diet compared to mice fed the regular rodent chow. However, there were no significant differences in body weight and blood glucose levels between the Wrn-deficient mice and Wrn-heterozygous mice fed the Surwit diet. These data suggest that, although there are undetectable differences in body weight and blood glucose levels in Wrn-deficient mice compared to Wrn-heterozygous mice fed the Surwit diet, the Wrn-deficiency or mutation may further elucidate underlying mechanisms for the aging process and the development of pre-diabetic conditions caused by high-fat, high-carbohydrate diets.

Methods

Study Group

The Wrn-deficient mice were backcrossed to C57BL/6J for five generations and then interbred to produce the Wrn −/− and heterozygous littermates used here. Mice used for this study were aged matched between 16–20 weeks of age.

Design

Ten WRN (−/−) and 10 Wrn (+/−) mice were fed a high fat, high sucrose "Surwit" diet containing 35.5% lard, 32.7% table sugar, and 20% protein. Control Wrn(−/−) mice, as well as control Wrn(+/−) mice, were fed regular rodent chow (4% fat). For all experiments, mice were given free access to food and water. Twice a week, the body weight was determined in mice. In addition, blood was drawn by retro-orbital sinus and by tail puncture. Blood glucose levels were determined by ACCU-Chek Advantage glucometer (Roche, Indianapolis, IN) according to

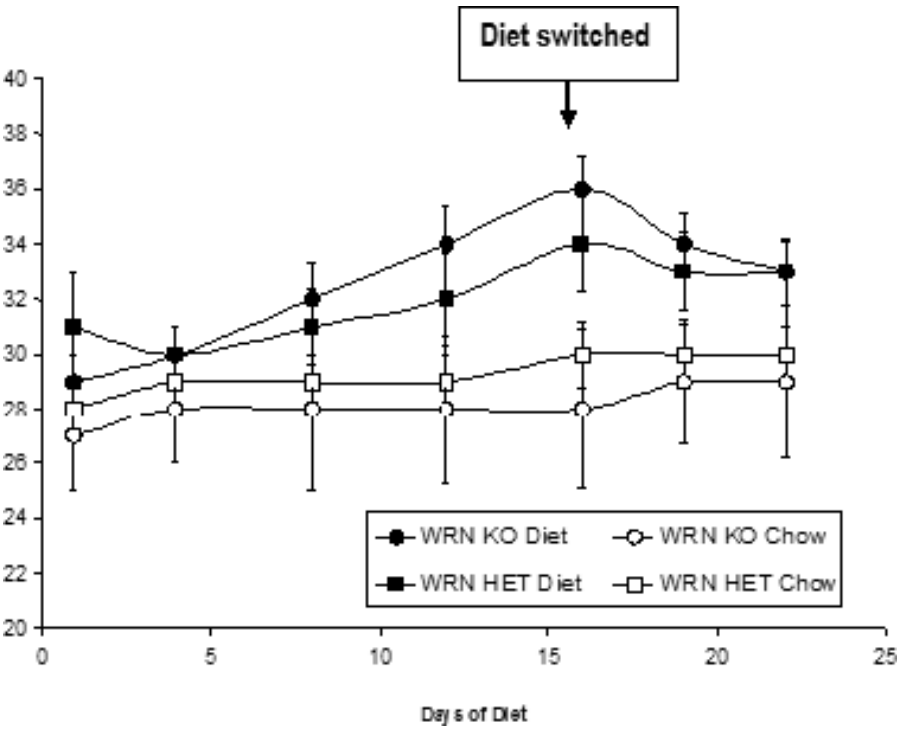

Fig 1. Body weights for male WRN (−/−) and WRN (+/−) mice fed high-fat, high-sucrose (Surwit) and regular rodent chow diets. Mice were introduced to the Surwit diet at 16–20 weeks of age. Body weights of WRN (−/−) mice (closed circles) were increased relative to those of WRN (+/−) mice (closed squares) when fed the Surwit diet for 16 days. Body weights of WRN (−/−) mice (closed circles) decreased relative to those of WRN (+/−) mice (closed squares) when changed to regular rodent chow after sixteen days

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manufacturer's instructions and the measurement range for blood glucose monitoring is from 10–600 mg/dL. After 16 days of diet treatment, all mouse diets were switched to regular rodent chow (4% fat) and the body weights and blood glucose levels were determined as previously described above for 6 days.

Statistics

Data are presented as means ±SD. Differences between genotypes were determined using the Student's *t* test. $P<.05$ was accepted as statistically significant.

RESULTS

Longitudinal Analysis of Body Weight Changes in Wrn(−/−) Mice (Figure 1)

All the mice tested had relatively similar body weights on day one through eight. After 12 days of feeding on the Surwit diet, the mean body weights in the Wrn(−/−) mice were significantly increased compared to those mice fed the regular chow diet (34 ± .4 vs 28 ± 2.7 g; $P<.03$). Similarly, the mean body weights in the Wrn(+/−) mice fed the Surwit diet were significantly increased compared to mice fed the regular chow diet (32 ± 1.7 vs 29 ± 1 g; $P<.03$). These data suggest that body weight increases in Wrn(−/−) mice and Wrn(+/−) mice after 12 days of feeding the Surwit diet. After 16 days of feeding the Surwit diet, the differences in mean body weights remained significantly increased between the Surwit-fed mice vs the chow-fed mice for both genotypes. When the Surwit-fed mice were changed to the regular rodent chow on day 16, surprising results occurred on day 19. The body weights of the previously Surwit-fed mice remained significantly increased compared to mice fed the regular chow diet. By day 22 (after 6 days of feeding the regular rodent chow), the body weights of the previously Surwit-fed mice still remained significantly increased. These data suggest that after 6 days of feeding regular rodent chow diet when previously being fed the Surwit-diet, the body weights of Wrn mice remain significantly increased and do not return to similar levels as measured on day one.

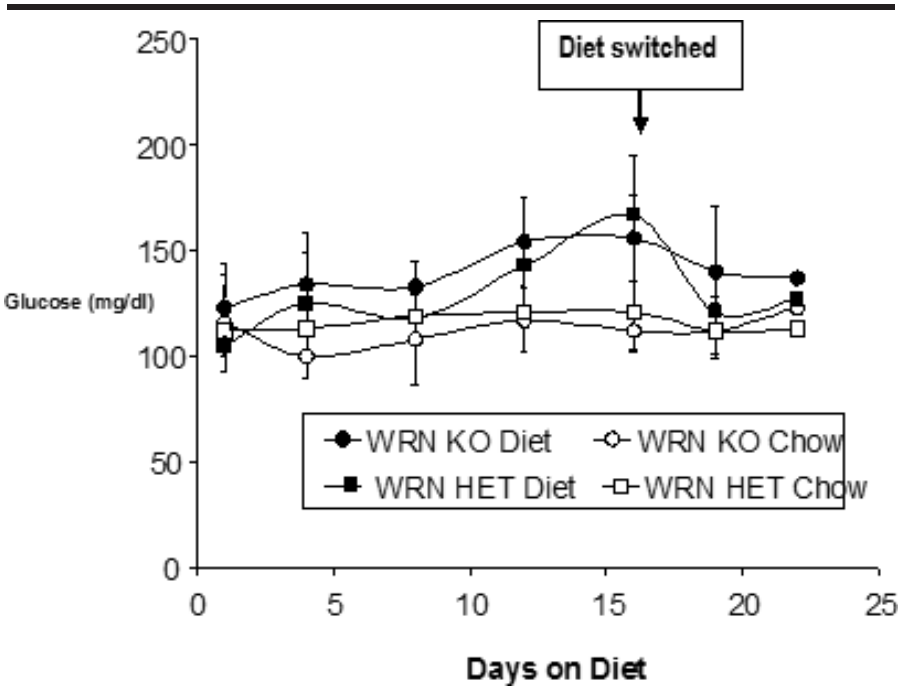

Fig 2. Glucose levels for male WRN (−/−) and WRN (+/−) mice fed a high-fat, high-sucrose (Surwit) and regular rodent chow diets. Glucose levels were significantly different between the genotypes at day 4 ($P<.05$) compared to rodent chow fed mice

Longitudinal Analysis of Wrn(−/−) Mice for Changes in Blood Glucose Levels (Figure 2)

All mice tested had relatively similar blood glucose levels on day one through eight of this experiment with the exception of day 4 for those feeding on the Surwit diet. On this day, the blood glucose levels significantly increased in Wrn(−/−) mice compared to those feeding on the regular chow diet (134 ± 25 vs 100 ± 10 mg/dL; $P<.03$). However by day eight, all mice had statistically similar blood glucose levels. By day 12 of feeding the Surwit diet, blood glucose levels in the Wrn(−/−) mice and Wrn(+/−) mice were significantly higher than for those fed the regular chow diet (154 ± 21 vs 117 ± 15 mg/dL; $P<.006$ for Wrn(−/−) mice and 143 ± 8.5 vs 121 ± 6.4 mg/dL; $P<.002$ for Wrn(+/−) mice; respectively). The blood glucose levels were not significantly different in Wrn(−/−) and Wrn(+/−) mice fed the Surwit diet ($P=.318$). After 16 days of feeding on the Surwit diet, blood glucose levels remained significantly increased in the Surwit-fed mice vs the chow-fed mice for both genotypes. The Surwit-fed mice were changed to the regular rodent chow on day 16 and, on day 19, no significant differences in blood glucose levels were found. These data suggest that within 3 days of feeding the regular rodent chow to mice previously fed the Surwit diet, the blood glucose levels re-

turn to similar levels observed on day one of feeding the Surwit diet.

DISCUSSION

This study demonstrates that the Surwit diet increases body weight and blood glucose levels in Wrn(−/−) and Wrn(+/−) mice after 12 days of feeding (Figures 1 and 2). In addition, we found that when the previously Surwit-fed mice were switched back to the regular rodent chow for 6 days, the body weights do not return to similar levels as determined on day one of feeding the Surwit diet (Figure 1). Whereas, when previously Surwit-fed mice were fed regular rodent chow, the blood glucose levels returned to start-up levels by day 3 (Figure 2). These data suggest that the Surwit-diet affects body weights and blood glucose levels in mice in less than two weeks. However, weight reduction is not observed when mice are fed a low-fat, low-carbohydrate diet even though blood glucose levels have decreased. The Surwit diet may have undetectable effects on mice on the Surwit diet and with the Wrn-deficient background because there were no significant differences observed between the Wrn(−/−) mice and the Wrn(+/−) mice in body weight and blood glucose levels. However, it may be that the Wrn(−/−) mice might have a more rapid increase in body weight and blood glucose levels compared to the Wrn(+/−) mice. Although the increases in body weight and blood glucose levels were significantly different by day 12 of feeding on the Surwit diet, the mice were not hyperglycemic as measured by the blood glucose levels.

Overall, this study suggests that Wrn-deficiency in mice may modulate weight gain and blood glucose levels when fed the Surwit diet. It remains to be determined if weight gain can be uncoupled from increases in blood glucose levels because Wrn mice switched back to regular rodent chow after being fed the Surwit diet did have similar levels of blood glucose, but the body weights remained significantly increased. These results suggest that within Wnr-deficient mice, environmental stressors, eg, high-fat, high-carbohydrate diet, may be a predisposing factor in the development of diabetes.

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