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Effects of KDT501 on Metabolic Parameters in Insulin-Resistant Prediabetic Humans

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Context: KDT501 is an isohumulone drug that has demonstrated beneficial effects on metabolic parameters in mice.

Objective: This study was intended to examine potential improvements in metabolism in humans.

Design and Setting: Changes in carbohydrate and lipid metabolism, along with inflammatory markers, were evaluated in prediabetic humans in a clinical research center.

Participants: Nine obese patients participated. All had prediabetes or normal glucose tolerance plus three features of metabolic syndrome.

Intervention: All participants were treated with escalating doses of KDT501 to a maximum dose of 1000 mg every 12 hours for a total of 28 days.

Outcome Measures: Changes in carbohydrate metabolism were measured with oral glucose tolerance, homeostatic model of insulin resistance, and euglycemic clamp; changes in plasma lipids and response to a lipid tolerance test; and changes in plasma inflammatory markers.

Results: The drug was well tolerated. After KDT501 treatment, plasma triglycerides were reduced at 4 hours during a lipid tolerance test. Furthermore, plasma adiponectin and high-molecular-weight adiponectin increased significantly, and plasma tumor necrosis factor-α decreased significantly. There were no significant changes in oral glucose tolerance test results or insulin sensitivity measures.

Conclusions: Despite the small sample size and the short duration of therapy, KDT501 administration reduced measures of systemic inflammation and improved postmeal plasma triglyceride levels, which may be beneficial in participants with insulin resistance or metabolic syndrome.

Freeform/Key Words: KDT501, insulin resistance, obesity, adiponectin

Obesity is associated with insulin resistance and chronic inflammation [1, 2], often culminating in the development of type 2 diabetes mellitus (T2DM). With expansion of fat mass and increasing adipocyte volume, considerable tissue remodeling is required, and the adipose tissue from obese, insulin-resistant rodents and humans is characterized by an increase in adipose inflammation [3–6]. One prevailing hypothesis suggests that adipocyte enlargement results in failed microvasculature expansion, with subsequent hypoxia, adipocyte necrosis,

Abbreviations: $AUC_{0\text{-}12}$, area under the curve at 0 to 12 hours; BMI, body mass index; FDA, US Food and Drug Administration; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LPS, lipopolysaccharide; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-α.

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infiltration of inflammatory cells, and macrophages forming crown-like structures surrounding the necrotic adipocyte, followed by a cycle of inflammatory changes, altered adipokine secretion, and changes in the extracellular matrix [7–9].

This study was designed to examine the possible efficacy and mechanism of action of KDT501 in insulin-resistant participants. KDT501 is the potassium salt of the *n*-(isobutyl) congener of a tetrahydro iso-α acid, also known as an isohumulone. In previous animal studies, a mixture of compounds derived from hops demonstrated anti-inflammatory activity and reductions in blood glucose [10, 11], along with a reduction in weight and plasma lipopolysaccharide (LPS) and an increase in thermogenesis [12, 13]. KDT501 was subsequently isolated from a hops mix and was determined to reduce inflammation, blood glucose, and triglycerides in rodents [14].

Together, these properties of KDT501 suggested complex but potentially favorable effects on multiple features of the insulin resistance/metabolic syndrome. This study therefore presents phase 1 data with KDT501 and then examines the effects of 4 weeks of treatment with escalating doses of KDT501 in insulin-resistant humans, with measurements of inflammatory and metabolic features, along with glucose and lipid metabolism. A secondary aim was the assessment of the safety and pharmacologic profile of KDT501.

1. Methods

A. Phase 1 Studies

A randomized, double-blinded, placebo-controlled, two-part phase 1 study was performed in healthy persons to investigate the safety, tolerability, and pharmacokinetics of KDT501. Exposure was limited to 20,800 ng · h/mL, consistent with exposure observed in the most sensitive toxicology species, rodents. Part 1 consisted of a sequential single oral dose-rising study in a total of 27 participants in four cohorts. Cohort 1 consisted of four participants (three active and one placebo); cohorts 2 and 3 comprised seven and eight participants (six active and one or two placebo), respectively; and cohorts 4a and 4b were composed of eight participants (six active and two placebo). They were administered KDT501 or placebo as oral enteric coated capsules at dose levels of 200, 400, and 800 mg for cohorts 1 through 3, respectively, and 600 mg with or without food for cohorts 4a and 4b. All participants were aged18 to 54 years inclusive, with a body mass index (BMI) of 21.7 to 31.7 kg/m^2, inclusive. Sixteen participants were male and 11 were female.

There were no deaths; no serious adverse events, other important adverse events, or substantial laboratory abnormalities were observed. No participants discontinued participation during this study. The most common treatment-related adverse event reported after administration of KDT501 at doses of 400, 600, and 800 mg was nausea (two events in two participants). Overall, single oral doses of KDT501 were well tolerated when administered in the fasted or fed states to healthy male and female participants.

After a single-dose administration of 200, 400, 600, and 800 mg KDT501 under fasted conditions, KDT501 was readily absorbed and steadily cleared. The mean half-life appeared to be dose dependent, with a trend of increasing half-life with increasing dose. Food slightly delayed absorption of KDT501.

Part 2 of the phase 1 trial consisted of a randomized, double-blind, placebo-controlled multiple ascending-dose study in a total of 27 participants in three cohorts. All cohorts consisted of nine participants (seven active and two placebo) dosed at 300, 600, or 800 mg KDT501 twice daily for 7 days. They were administered KDT501 or placebo as oral enteric coated capsules. The participants were aged 18 to 55 years inclusive, with a BMI between 21.8 and 30.6 kg/m^2, inclusive. Nineteen participants were male and eight were female.

Multiple oral doses of KDT501 were considered to be safe and well tolerated by healthy male and female participants for 7 days in the fed state. There were no deaths or serious adverse events reported during the study. There were no treatment- or dose-related trends and no clinically important findings for individual participants during the study. All

treatment-emergent adverse events reported were mild except for one moderate report of upper abdominal pain. The most common treatment-emergent adverse event reported was headache (one event in seven participants).

KDT501 was readily absorbed and steadily eliminated after multiple dosing under fed conditions. Mean half-life values appeared to increase with dose and were dose dependent on day 7. Increases in maximum concentration and area under the curve at 0 to 12 hours ($AUC_{0\text{-}12}$) were dose proportional on day 7. Steady-state concentrations of KDT501 appeared to have been achieved by day 6 of the study. The mean (standard deviation) $AUC_{0\text{-}12}$ that was achieved at the end of the 7-day treatment period at 600 mg twice daily was 7555 ± 3000 ng · h/mL.

On the basis of the previously-described phase 1 studies, involving a total of 54 normal healthy volunteers who were treated with KDT501 at doses up to 800 mg twice daily for a maximum of 7 days, a phase 2 study was designed to determine a mechanism of action for KDT501 within the limits of exposure prescribed by the US Food and Drug Administration (FDA). For this phase 2 study, the target population was nondiabetic participants with insulin resistance or participants with metabolic syndrome, who were to be treated with open-label escalating doses of KDT501, to a maximum of 1000 mg twice daily, for a maximum of 28 days of treatment.

B. Human Participants and Study Design

All participants gave informed consent, and the Institutional Review Board at the University of Kentucky approved the protocol and amendments. This study enrolled a total of nine participants (two men and seven women) with insulin resistance who had not been previously treated with any medications for diabetes. All participants had a BMI >27 kg/m^2 (mean BMI, 37.3 ± 1.2 kg/m^2), were 40 to 70 years old (mean age, 53.4 ± 2.8 years), and had impaired glucose tolerance (IGT), impaired fasting glucose (IFG) (based on a standard 75-g oral glucose tolerance test), or three features of metabolic syndrome [15]. Of these nine participants, eight qualified on the basis of IGT and/or IFG and one had normal glucose tolerance but qualified according to criteria for metabolic syndrome. Other key eligibility criteria included (1) no history of diabetes; (2) hemoglobin A1c <7.0% and fasting glucose <126 mg/dL within 28 days of trial initiation; and (3) no significant cardiovascular, pulmonary, or gastrointestinal disorders. Two patients would qualify as diabetic according to some, but not all, criteria. One patient had a hemoglobin A1c value of 6.8%, but the oral glucose tolerance test (OGTT) result was consistent with IFG/IGT. One patient had a 2-hour glucose of 220 mg/dL but a hemoglobin A1c value of only 6.2%. Some of these participants were taking medications for hypertension; the mean blood pressure was 135/87 mm Hg. Two participants were taking a statin.

Potential study participants were recruited through advertising and reported in a fasting state to the initial visit, which included the OGTT. After participants were deemed eligible, additional baseline testing included dual-energy x-ray absorptiometry for body composition, resting metabolic rate, a lipid tolerance test for measurement of plasma LPS and triglyceride, fasting blood for plasma cytokines, and a euglycemic clamp for measurement of insulin sensitivity. All studies were performed in the Clinical Research Unit of the University of Kentucky.

On the basis of a prior agreement with FDA, each patient could receive KDT501 for a maximum of 28 days, with limits on drug exposure as measured by $AUC_{0\text{-}12}$. Each participant received KDT501 at a starting dose of 600 mg twice daily. On day 7, pharmacokinetics were performed. Participants reported fasting and took their 600-mg dose of KDT501 with a meal; blood was obtained at time 0, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, and 12 hours for measurement of plasma KDT501 (Medpace Bioanalytical Laboratories, Cincinnati, OH). On the basis of the $AUC_{0\text{-}12}$ (not to exceed 22,500 ng · h/mL), the dose was escalated to 800 mg twice daily. On day 17, a repeat pharmacokinetics study was performed on the 800-mg twice-daily dose, and the dose was again escalated, to 1000 mg twice

daily, as long as the AUC was within acceptable limits. Of the nine participants studied, five had dose escalation to the maximal dose of 1000 mg twice daily, three finished the 28-day study at a maximal dose of 800 mg twice daily, and one remained at a dose of 600 mg twice daily for the entire 28-day period. No participants required a dose reduction, and no participants discontinued treatment before the 28-day maximum. Among all nine participants, the mean (standard error of the mean) $AUC_{0\text{-}12}$ that was achieved at the end of the 28-day treatment period was 14,047 (2941) ng · h/mL.

The primary endpoint for the study was the change in 2-hour OGTT result, defined as the median change in plasma glucose 2 hours after the consumption of the 75-g oral glucose challenge at day 28 vs baseline. Secondary endpoints included changes from baseline in lipid tolerance, hemoglobin A1c, fasting plasma glucose, plasma insulin, insulin sensitivity measures, and selected inflammatory markers.

C. Lipid Tolerance Test

In addition to measuring fasting lipids, a lipid tolerance test was performed at baseline and after 28 days of treatment with KDT501. Participants reported after a 12-hour fast, having refrained from alcohol, and consumed a high-fat breakfast shake, consisting of Boost (Nestlé, Arlington, VA) with added cream and corn oil in a fixed proportion to provide a mix of fatty acids typical of a U.S. diet (palmitate 16:0, 28%; stearate 18:0, 12%; oleate 18:1, 21%; linoleate 18:2, 26%), as described previously [16]. Daily energy requirement was calculated by using the Harris–Benedict equation; the high-fat shake encompassed 40% of their daily energy requirements and was 50% fat. The meal was consumed within 15 minutes, and blood was drawn hourly for 4 hours. From the baseline and hourly samples after the fat meal, triglycerides were measured by using the Triglyceride Liquid Assay (T7532; Pointe Scientific, Canton, MI). For the LPS assays, we collected blood in citrate, diluted the citrated plasma 1:5 in endotoxin-free water (Lonza, Basel, Switzerland), heat inactivated the sample at 70°C for 10 minutes, and stored the samples at −80°C. We then treated the samples with an Endotoxin Sample Preparation kit (BioDtech, Inc., Birmingham, AL) and performed LPS assays with the ToxinSensor kit (L00350; Genscript, Piscataway, NJ). The final dilution factor was 1:110. Because triglycerides and other components of blood can interfere with the assay [17], we performed a control reaction with no limulus amoebocyte lysate enzyme. These controls were all below the detection limit of the assay, indicating that the large dilution minimized interference with the assay.

D. Euglycemic Clamp

Peripheral insulin sensitivity was measured with a euglycemic clamp to assess peripheral glucose disposal rate as an index of insulin sensitivity. Participants reported fasting to the Clinical Research Unit, and peripheral intravenous infusions were started (including a retrograde intravenous line in a warming box and an antecubital line for infusions). After a 30-minute period of baseline stabilization, an insulin infusion started at 1 mU/kg per minute, along with a 20% glucose solution at a variable rate to maintain euglycemia for 2 hours. Blood glucose was measured every 5 to 10 minutes and blood insulin, every 10 minutes during the final 30 minutes of the procedure. Glucose disposal (glucose infusion rate) was determined during steady-state glucose during the final 30 minutes of the procedure.

E. Plasma Cytokines and Insulin

Plasma cytokines were measured by using Luminex assays (ThermoFisher Scientific, Waltham, MA) employing the Milliplex cytokine high-sensitivity assay (EMD Millipore, Billerica, MA), the human metabolic hormone assay, and adipokine A assay kits. Total and high-molecular-weight adiponectin were measured by using a Multimeric Adiponectin enzyme-linked immunosorbent assay kit (Alpco, Salem, NH). Insulin was measured in plasma samples with an immunochemiluminescence assay (Alpco).

F. Other Procedures

Body composition was determined by using dual-energy x-ray absorptiometry. For measurement of resting metabolic rate, the patient reported early in the morning, fasting. A hood was placed over the face in a quiet room, and CO_2 exhaled and O_2 consumed were measured by breathing into a disposable tube on the metabolic cart. This process was continued until the CO_2 reached its nadir, for 15 minutes. This rate of CO_2 production is considered the resting metabolic rate.

G. Safety Measures

Other studies were performed to evaluate the safety profile of KDT501. These included frequent vital signs, adverse event evaluations, urinalysis, fecal occult blood testing, spirometry, electrocardiography, and routine blood tests (including hemography, coagulation testing, and comprehensive metabolic panel).

H. Statistics and Calculations

All data are expressed as mean ± standard error of the mean, and a paired *t* test was used to compare pre- vs post-KDT501 treatment. The homeostatic model of insulin resistance, Matsuda index, and insulinogenic index were calculated as described previously by using the values of glucose and insulin from the OGTT [18]. Disposition index was calculated as the product of insulin secretion and insulin sensitivity [insulinogenic index and Matsuda index (Graphpad Prism 5, La Jolla, CA), respectively].

2. Results

This study included nine participants who met all inclusion and exclusion criteria. All completed this study. The overall goal was to determine whether there were any trends toward improvement in carbohydrate or lipid metabolism and whether there were any changes in inflammatory markers after 28 days of treatment with KDT501 using the dose-escalation protocol described in Methods. During this 28-day treatment period, weight, percentage body fat, and blood pressure did not change significantly. The pre- and post-treatment weights were 100.8 ± 5.5 kg and 100.3 ± 5.7 kg, respectively.

A. Carbohydrate Metabolism

Glucose tolerance was assessed with a standard OGTT. As shown in Table 1, the mean fasting glucose level was not changed by KDT501 treatment. The 2-hour glucose levels were reduced from 171 ± 12 mg/dL to 162 ± 18 mg/dL. Although the values for 2-hour glucose after

Table 1. Changes in Carbohydrate Metabolism After Drug Treatment

Variable	Baseline	After KDT501 Treatment
Fasting glucose (mg/dL)	103 ± 4	103 ± 6
2-hour glucose (mg/dL)	171 ± 12	162 ± 18
Hemoglobin A1c (%)	5.87 ± 0.15	5.82 ± 0.16
Fructosamine (μM/L)	222 ± 8.8	217 ± 7.2
HOMA-IR	7.01 ± 1.4	6.25 ± 1.5
Matsuda index	1.51 ± 0.42	1.68 ± 0.26
Insulinogenic index	2.29 ± 0.72	2.74 ± 1.12
Glucose infusion rate (mg/min per kg)	2.46 ± 0.53	2.44 ± 0.52

Values are expressed as mean ± standard error of the mean.
Abbreviations: HOMA-IR, homeostatic model of insulin resistance.

treatment were not statistically different from baseline, the reduced 2-hour glucose is consistent with the potential for KDT501 to improve glucose tolerance if given for a more prolonged period, and/or if evaluated in more participants. Hemoglobin A1c and glycosylated albumin (fructosamine) did not change significantly (Table 1).

Insulin sensitivity was determined by using measures of glucose and insulin during the oral glucose tolerance test (homeostatic model of insulin resistance, Matsuda index), and additionally through the use of the euglycemic glucose clamp study, as described in Methods. As shown in Table 1, there were no significant changes in any measure of insulin sensitivity using these measures. In addition, assessment of insulin secretion using the insulinogenic index showed no significant change, and disposition index did not significantly change.

B. Lipid Metabolism

As noted in Table 2, fasting plasma triglycerides did not change after KDT501 treatment; however, there was a statistically significant decrease in total cholesterol. This decrease in total cholesterol was primarily due to a nonsignificant trend for a decrease in low-density lipoprotein cholesterol from 110 ± 10 mg/dL to 102 ± 11 mg/dL ($P = 0.10$).

To further assess the dynamics of lipid metabolism, a lipid tolerance test was performed, with measurement of plasma triglycerides and LPS during fasting and then again after a standardized fatty meal. The fasting and 4-hour postmeal plasma triglyceride levels are shown in Table 2. KDT501 treatment did not decrease fasting triglyceride levels but significantly decreased 4-hour triglyceride (from 185 ± 13 mg/dL to 155 ± 13 mg/dL; $P < 0.05$) after the lipid meal. Baseline LPS levels and LPS levels 4 hours after the lipid meal did not change (Table 2).

C. Plasma Cytokines and Adipokines

Table 3 includes the levels of several inflammatory markers and adipokines. Statistically significant changes after treatment with KDT501 included an increase in both total and high-molecular-weight adiponectin, along with a significant decrease in plasma tumor necrosis factor-α (TNF-α). Other inflammatory markers (serum amyloid A, interleukin-6, C-reactive protein, and monocyte chemoattractant protein-1), along with fibrinogen and zonulin, did not change significantly.

D. Safety and Adverse Events

Treatment with KDT501 was generally well tolerated. Eight of the nine study participants experienced an adverse effect judged to be possibly related to the study drug, all of which were graded as mild or moderate. In no case was it necessary to stop the drug or alter the dose, and

Table 2. Changes in Lipid Metabolism After Drug Treatment

Variable	Baseline	After KDT501 Treatment
Cholesterol (mg/dL)	186 ± 12.3	176 ± 12.1[a]
Triglyceride (mg/dL)	132 ± 17.9	124 ± 14.8
HDL-C (mg/dL)	49 ± 5.8	48 ± 6.8
LDL-C (mg/dL)	110 ± 9.6	102 ± 11.1
Postmeal TG (mg/dL)	185 ± 12.7	155 ± 12.7[a]
LPS (EU/mL)	0.44 ± 0.09	0.56 ± 0.17
Postmeal LPS (EU/mL)	2.1 ± 0.3	1.8 ± 0.3

Values are expressed as mean ± standard error of the mean.
Abbreviations: EU, endotoxin units; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a] $P < 0.05$ vs baseline.

Table 3. Effects of KDT501 on Plasma Cytokines and Adipokines

Variable	Baseline	After KDT501 Treatment
Adiponectin (μg/mL)	2.99 ± 0.25	3.30 ± 0.20[a]
HMW adiponectin (μg/mL)	1.34 ± 0.17	1.53 ± 0.52[a]
CRP (μg/mL)	6.87 ± 1.30	7.94 ± 1.78
LBP (ng/ml)	29.3 ± 2.40	29.7 ± 1.76
SAA (ng/mL)	47.2 ± 9.37	40.0 ± 6.03
TNF-α (pg/mL)	3.29 ± 0.31	3.09 ± 0.27[a]
IL-6 (pg/mL)	1.24 ± 0.18	1.39 ± 0.35
MCP-1 (pg/mL)	316 ± 37.7	298 ± 33.3
Zonulin (ng/mL)	2.37 ± 0.13	2.49 ± 0.11
Fibrinogen (ng/mL)	212 ± 9.5	204 ± 5.8

Values are expressed as mean ± standard error of the mean.
Abbreviations: CRP, C-reactive protein; HMW, high-molecular-weight; IL-6, interleukin-6; LBP, lipopolysaccharide binding protein; MCP-1, monocyte chemoattractant protein-1; SAA, serum amyloid A.
[a] $P < 0.05$ vs baseline.

these side effects resolved spontaneously. These adverse events were mostly gastrointestinal effects, including abdominal discomfort, diarrhea, or symptoms of esophageal reflux. Most of these participants reported a history of similar symptoms in the past. The most common adverse events were diarrhea (four participants); positivity for fecal occult blood (three participants); and headache, rash, and vomiting (two participants each). There was no evidence of greater toxicity with higher serum levels of KDT501. In all three participants with positivity for fecal occult blood, the finding had other explanations (*e.g.,* known hemorrhoids); all three had subsequent negative test results, and KDT501 dosing was not changed or interrupted.

No significant treatment or dose-related findings were noted in the clinical laboratory evaluations, physical examinations, or pulmonary function assessments (data not shown). Laboratory review showed no evidence of hepatic, renal, or bone marrow toxicity.

3. Discussion

KDT501 is the potassium salt of a substituted 1,3-cyclopentadione, chemically derived from hop extracts and a member of the isohumulone class of compounds (chemical structure in Fig. 1). This human study was undertaken because of the promising findings with hops-derived compounds, and with KDT501, on features of the metabolic syndrome and insulin resistance in previous rodent and *in vitro* studies.

Some previous studies used a mixture of compounds that derived from hops. These compounds had a history of use as bittering additives in beer and were on the FDA's "generally recognized as safe." A formulation known as META060 was shown to inhibit nuclear factor-κB

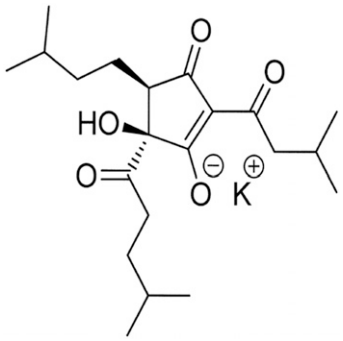

Figure 1. The structure of KDT501.

activation in cultured macrophages; it was bioavailable when given to humans [11], and reduced weight gain and improved blood glucose and metabolic flexibility when given to high-fat-fed mice [12, 13]. More recently, KDT501 was developed and was found to decrease the expected gain of body weight of ZDF rats, and also reduced hemoglobin A1c, blood glucose, and plasma triglycerides [14]. After the observation that KDT501 was well tolerated after a single dose of 200 to 800 mg in a phase 1 trial (KinDex Pharmaceuticals, unpublished data), this study was undertaken to determine whether any metabolic benefit would be observed.

Because the rodent studies noted improvements in carbohydrate and lipid tolerance, along with potential anti-inflammatory actions, this study focused on the results of an OGTT, lipid levels, and inflammatory markers. Rodent studies also noted improvements in body weight. However, this human study was not allowed to progress beyond 28 days, and therefore a change in weight was not a primary objective. Changes in glycemic control (such as hemoglobin A1c) would also not be expected to occur in a short time frame. Therefore, measurements were made that were believed to suggest mechanistic effects of KDT501 and that may precede an eventual improvement in blood glucose. These mechanistic studies included a high-dose euglycemic clamp, along with the measurement of postmeal triglyceride and of inflammatory markers.

As described previously, no significant changes in the OGTT data were noted, nor were there changes in hemoglobin A1c. In addition, measures of insulin resistance (including the Matsuda index and the homeostatic model of insulin resistance) did not improve, nor did peripheral insulin sensitivity using a high-dose euglycemic clamp. Although KDT501 did not improve markers of insulin sensitivity, this study involved only 28 days of treatment, starting at a low dose. The 2-hour glucose value after the OGTT was lower, although not significantly. This could indicate that the full effect of KDT501 may take longer, and the optimal dose has not yet been determined. In addition, this study did not specifically evaluate hepatic insulin sensitivity, which could potentially be a target of KDT501.

Numerous studies have documented the important role of chronic inflammation in the pathophysiology of metabolic syndrome and T2DM [2]. Among the most important markers of the dysmetabolism of metabolic syndrome is adiponectin, which is secreted from adipose tissue and is lower in obesity, inversely correlating with chronic inflammation and cardiovascular disease [19]. Adiponectin undergoes substantial posttranscriptional processing, forming aggregates, and the high-molecular-weight form of adiponectin has been most closely associated with the insulin-sensitizing and anti-inflammatory properties [20, 21]. Another feature of metabolic syndrome and T2DM is activation of type 1 inflammatory markers, such as TNF-α [22, 23] and the infiltration of adipose tissue by macrophages and other cells of the immune system [24–26].

As described previously, KDT501 treatment of insulin-resistant participants resulted in a significant increase in both total and high-molecular-weight adiponectin and a significant decrease in TNFα. The precise mechanism for this effect of KDT501 is not known. Because adiponectin is essentially exclusively expressed by adipocytes, these studies would suggest that KDT501 results in improved adipose function, which may also result in other anti-inflammatory effects leading to a decrease TNF-α. It would be of interest to know whether longer treatment with KDT501 would have a sustained anti-inflammatory effect, which would then result in improved insulin sensitivity.

Another improvement in metabolism noted from these studies was an improvement in lipid metabolism. Fasting plasma lipids were not significantly altered by KDT501. Low-density lipoprotein cholesterol was decreased from 110 ± 9.6 mg/dL to 102 ± 11.1 mg/dL, but this was not statistically significant. However, postmeal triglyceride did significantly decrease. The decreased postmeal triglyceride could be due to increased triglyceride-rich lipoprotein clearance by lipoprotein lipase, again implicating an effect in adipose tissue, which is a primary source of lipase activity.

In summary, KDT501 is a class of drug that is well tolerated and that appears, from these limited data in nine insulin-resistant participants, to have anti-inflammatory properties and improved postabsorptive lipid metabolism. Further studies are warranted to better

determine the mechanism of action of this drug and to determine whether longer-term treatment with appropriate doses will improve established clinical features of the dysmetabolism that leads to T2DM in humans.

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