fructose by KHK is associated with diseases, disorders or conditions such as liver disease (*e.g.*, fatty liver, steatohepatitis), dyslipidemia (*e.g.*, hyperlipidemia, high LDL cholesterol, low HDL cholesterol, hypertriglyceridemia, postprandial hypertriglyceridemia), disorders of glycemic control (*e.g.*, insulin resistance, type 2 diabetes), cardiovascular disease (*e.g.*, hypertension, endothelial cell dysfunction), kidney disease (*e.g.*, acute kidney disorder, tubular dysfunction, proinflammatory changes to the proximal tubules, chronic kidney disease), metabolic syndrome, adipocyte dysfunction, visceral adipose deposition, obesity, hyperuricemia, gout, eating disorders, and excessive sugar craving.

Accordingly, there is a need in the art for compositions and methods for treating diseases, disorders, and conditions associated with KHK activity.

Summary of the Invention

In one aspect, provided herein is a double stranded ribonucleic acid (dsRNA) for inhibiting expression of ketohexokinase (KHK) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from the nucleotide sequence of nucleotides 1209-1229 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 2.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) for inhibiting expression of ketohexokinase (KHK) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding KHK, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-5.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) for inhibiting expression of ketohexokinase (KHK) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 943-965; 788-810; 734-756; 1016-1038; 1013-1035; 1149-1171; 574-596; 1207-1229 or 828-850 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

In another aspect, provided herein is a cell containing the dsRNA agent as described herein.

In another aspect, provided herein is a pharmaceutical composition for inhibiting expression of a gene encoding ketohexokinase (KHK) comprising the dsRNA agent as described herein.

In another aspect, provided herein is the use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for inhibiting expression of a ketohexokinase (KHK) gene in a cell, wherein the cell is to be contacted with the

dsRNA agent as described herein, or the pharmaceutical composition as described herein, thereby inhibiting expression of the KHK gene in the cell.

In another aspect, provided herein is use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in ketohexokinase expression, wherein a therapeutically effective amount of the dsRNA agent as described herein, or the pharmaceutical composition as described herein is to be administered to the subject, thereby treating the subject having the disorder that would benefit from reduction in ketohexokinase expression.

In another aspect, provided herein is use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for preventing at least one symptom in a subject having a disorder that would benefit from reduction in ketohexokinase expression, wherein a prophylactically effective amount of the dsRNA agent as described herein, or the pharmaceutical composition as described herein is to be administered to the subject, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in ketohexokinase expression.

In another aspect, provided herein is a kit comprising the dsRNA agent as described herein or the pharmaceutical composition as described herein.

In another aspect, provided herein is a vial comprising the dsRNA agent as described herein or the pharmaceutical composition as described herein.

In yet another aspect, provided herein is a syringe comprising the dsRNA agent as described herein or the pharmaceutical composition as described herein.

In yet another aspect, provided herein is the dsRNA agent as described herein or the pharmaceutical composition as described herein for use in therapy.

The present invention provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding ketohexokinase (KHK). The ketohexokinase (KHK) may be within a cell, *e.g.*, a cell within a subject, such as a human subject.

In an aspect, the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of ketohexokinase in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:2.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of ketohexokinase in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding ketohexokinase, and wherein the region of

complementarity comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-5.

In one aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of ketohexokinase in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 943-965; 788-810; 734-756; 1016-1038; 1013-1035; 1207-1229; 1149-1171; 574-596; 1207-1229 or 828-850 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than 0, 1, 2, or 3 nucleotides from any one of the antisense strand nucleotide