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Xiu-Xia Song, Vice Director
World Journal of Diabetes
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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PUBLISHER
Baishideng Publishing Group Inc
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Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
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REVIEW

Pharmacogenetic studies update in type 2 diabetes mellitus

Shalini Singh, Kauser Usman, Monisha Banerjee

Shalini Singh, Monisha Banerjee, Molecular and Human Genetics Laboratory, Department of Zoology, University of Lucknow, Lucknow 226007, India

Kauser Usman, Department of Medicine, King George's Medical University, Lucknow 226003, India

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Correspondence to: Dr. Monisha Banerjee, Professor, Molecular and Human Genetics Laboratory, Department of Zoology, University of Lucknow, University Road, Lucknow 226007, India. banerjee_monisha30@rediffmail.com
Telephone: +91-98-39500439

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Abstract

Type 2 diabetes mellitus (T2DM) is a silent progressive polygenic metabolic disorder resulting from ineffective insulin cascading in the body. World-wide, about 415 million people are suffering from T2DM with a projected rise to 642 million in 2040. T2DM is treated with several classes of oral antidiabetic drugs (OADs) *viz.* biguanides, sulfonylureas, thiazolidinediones, meglitinides, etc. Treatment strategies for T2DM are to minimize long-term micro and macro vascular complications by achieving an optimized glycemic control. Genetic variations in the human genome not only disclose the risk of T2DM development but also predict the personalized response to drug therapy. Inter-individual variability in response to OADs is due to polymorphisms in genes encoding drug receptors, transporters, and metabolizing enzymes for example, genetic variants in solute carrier transporters (*SLC22A1*, *SLC22A2*, *SLC22A3*, *SLC47A1* and *SLC47A2*) are actively involved in glycemic/HbA1c management of metformin. In addition, *CYP* gene encoding Cytochrome P450 enzymes also play a crucial role with respect to metabolism of drugs. Pharmacogenetic studies provide insights on the relationship between individual genetic variants and variable therapeutic outcomes of various OADs. Clinical utility of pharmacogenetic study is to predict the therapeutic dose of various OADs on individual basis. Pharmacogenetics therefore, is a step towards personalized medicine which will greatly improve the efficacy of diabetes treatment.

Key words: Type 2 diabetes mellitus; Pharmacogenetics; Genetic variants; Oral antidiabetic drugs; Personalized medicine

Core tip: Type 2 diabetes mellitus (T2DM) is a highly prevalent metabolic disorder, characterized by chronic hyperglycemia. It results from an interaction of environmental as well as genetic factors. Several genes have been identified associated with disease development and therapeutic outcomes. Inter-individual variations in the human genome affect both, risk of T2DM development and personalized response to identical drug therapies. Pharmacogenetic approaches focus on single nucleotide polymorphisms and their influence on individual drug response, efficacy and toxicity. In the

present study, an effort has been made to review the genetic polymorphisms in candidate genes associated with efficacy of oral antidiabetic drugs.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) has been considered as a major health problem for both developed as well as developing countries. The global burden of diabetes is presently 415 million affected people, expected to rise to 642 million in 2040 and about 193 million people still undiagnosed. The Indian estimate is also alarming which shows 69.2 million people affected with T2DM in 2015 which will rise to 123.5 million in 2040[1].

Diabetes is traditionally known as a "silent disease" manifesting no symptoms until it progresses to severe damage of target organs. Diabetes has been classified under various categories depending upon their age of onset and severity[2]. The most prevalent adult-onset diabetes is T2DM characterized by hyperglycemia caused by defects in both insulin secretion and insulin signaling cascade. T2DM is a potential contributor to considerable morbidity in the form of metabolic complications *viz.* heart disease, stroke, neuropathy, kidney disease, vision disorder, peripheral vascular disease, ulcerations and amputations, infection, digestive diseases, oral complications and depression. T2DM is a multifactorial disease with high genetic variability in which certain candidate genes interfere with management of glycemic control in the body. Polymorphisms in the candidate genes may affect the susceptibility or risk of disease development and progression[3-7].

Pharmacogenomics establishes the use of an individual's genetic information to guide treatment therapy and has become an important tool in achieving "personalized medicine". The discoveries of novel genetic polymorphisms in drug transporters, and metabolizing enzymes have given an insight into the biological phenomena of drug efficacy and toxicity (Figure 1). Pharmacologically, several classes of drugs are currently being prescribed to treat T2DM patients, including biguanides, sulfonylureas, meglitinides, thiazolidinediones (TZDs), α-Glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonist, sodium-glucose co-transporter-2 inhibitors, insulin and its analogues[8-10]. Clinically, it is often observed that T2DM patients who receive identical antidiabetic regimens often exhibit significant variation in glycemic control, glycated haemoglobin (HbA1c) level, drug efficacy, tolerability and incidence of adverse effects[11]. Inter-individual differences can be attributed to polymorphisms of certain candidate genes involved in drug absorption, transportation, distribution, metabolism and signaling cascade of oral antidiabetic drugs (OADs)[11].

PHARMACOGENETICS

The term "pharmacogenetics" was coined by Vogel *et al*[12] which explains the differential response of individuals to identical medication. Clinical observations of inherited inter-individual differences during treatment were documented for the first time in 1950s[13-15] giving rise to a new field, *i.e.,* pharmacogenetics and later pharmacogenomics. Pharmacogenomics is being used for genome-wide approaches to recognize the inherited inter-individual differences in response to drugs. Pharmacogenetics reveals that single nucleotide variations in genes (encoding drug receptor, transporters and metabolizing enzymes) are related to the efficacy and toxicity of drugs[16-18], for example *CYP2D6*, *CYP2C8* and *CYP2C9* are marked *CYP* enzymes that are actively involved in metabolism of various therapeutic agents[19].

The inter-individual differences are contributed by numerous factors, *i.e.,* physical inactivity, race/ethnic diversity, hypertension, age, gender, *etc*[20]. During past decades, pharmacogenetic study was restricted to observations of familial response to a particular drug. However, genome-wide association studies, candidate gene approach and linkage analysis have transformed the area of pharmacogenetics/pharmacogenomics. These studies have elucidated the role of genetic variations for a particular drug and their doses on a personalized basis.

PHARMACOGENETICS OF T2DM IN PROSPECT WITH OADS

Treatment strategy for T2DM is mainly based on efficacy of OADs assessed by level of fasting/postprandial plasma glucose and/or HbA1c[10].

BIGUANIDES

Metformin (N',N'-dimethylbiguanide) is prescribed as a first-line medication for newly diagnosed T2DM patients[21]. Antihyperglycemic effects of metformin includes down regulation of hepatic gluconeogenesis, improvement in insulin sensitivity and significant reduction in insulin resistance[22]. The precise mechanism(s) of metformin action are still not fully elucidated. At physiological pH metformin serves as an organic cation being transported across the membrane by different isoforms of organic cation transporters (OCTs) *viz.* OCT1 expressed in hepatocytes, OCT2 in basolateral membrane of kidney. Metformin is transported from intestinal lumen into the epithelial cells *via* OCT3 and plasma membrane monoamine transporter. Uptake of metfomin from blood into hepatocytes is mediated

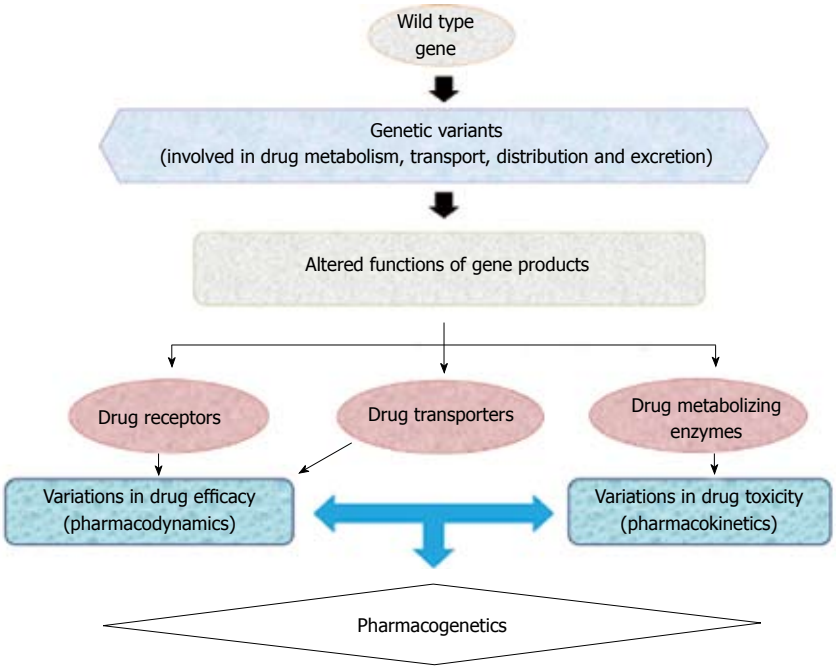

Figure 1 Effects of gene polymorphisms on drug efficacy and toxicity.

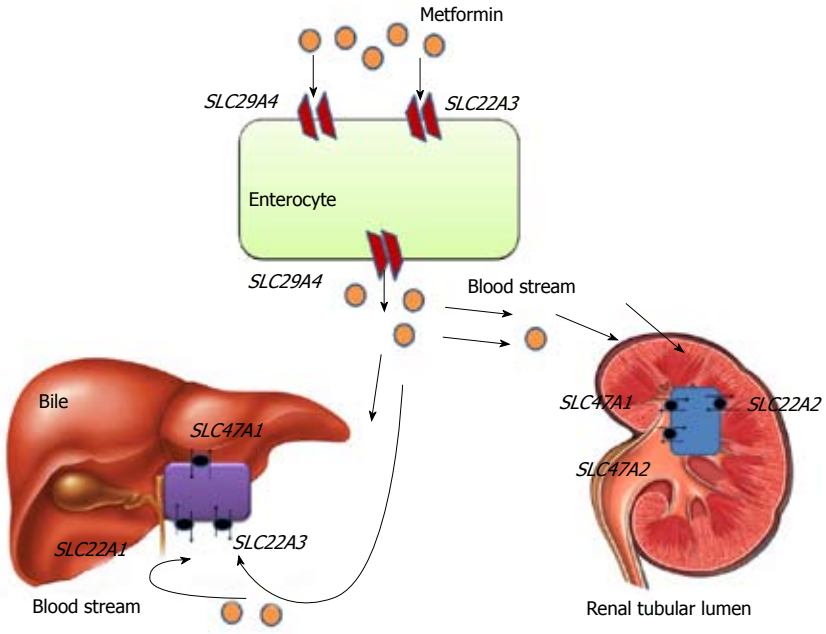

Figure 2 Schematic representation of cellular locations of metformin transporters. *SLC22A3*: Solute carrier family 22 member 3; *SLC29A4*: Solute carrier family 29 member 4.

by OCT1 and OCT3 (Figure 2). Metformin interferes with mitochondrial respiratory chain complex 1 by increasing AMP/ATP ratio, which promotes the activation of AMP kinase[23,24]. Metformin-induced AMP kinase activation leads to transcriptional inhibition of hepatic gluconeogenesis[25]. Metformin is not metabolized and excreted-out through urine *via* active renal tubular secretion. Metformin excretion in bile and urine is also facilitated by various isoforms of Multidrug and Toxin Extrusion transporters (MATE1 and MATE2)[26,27]. Therapeutic response of metformin differs inter-individually due to genetic polymorphisms. Single nucleotide polymorphisms (SNPs) in the genes encoding metformin transporters *viz.* OCT1, OCT2, MATE1, MATE2, *etc.*, leads to significant association with the different degrees of efficacy and toxicity (Figure 2).

GENES ASSOCIATED WITH BIGUANIDE TREATMENT

Solute carrier family 22 member 1

Solute carrier family 22 member 1 *(SLC22A1)* gene encodes the OCT1 which is expressed in hepatocytes and mediates the electrogenic transport of drugs[28]. OCT1 helps in transport of metformin into the liver (hepatocytes) and subsequent activity. It has been hypothesized that highly polymorphic *SLC22A1* gene will influence the therapeutic success rate of metformin. In a South Indian study[29], it was reported that rs622342

variant of *SLC22A1* gene was significantly associated with efficacy of metformin. They found that T2DM patients with rs622342 "AA" homozygotes had 5.6 times increased possibility of responding to metformin treatment. A recent pharmacogenetic study performed in a Chinese population demonstrated that T2DM patients with "AA" genotype of *SLC22A1* rs594709 might have maximum plasma glucose lowering effect from metformin monotherapy[30]. Shu *et al*[31] studied the effect of loss of function polymorphism in *SLC22A1* gene variants, *i.e.,* rs12208357 (R61C), rs34130495 (G401S), rs72552763 (420del), rs34059508 (G465R). They concluded the study as these variants were significantly associated with lower efficacy of metformin in glucose tolerance test. However, in a subsequent GoDARTs study, two common *SLC22A1* variants, R61C (rs12208357) and 420del (rs72552763) were reported to have no association with impaired initial response to metformin, or metformin monotherapy failure[32].

Solute carrier family 22 member 2

Solute carrier family 22 member 2 (*SLC22A2*) gene encodes the OCT2. OCT2 is a drug transporter and expressed in renal tubular cells thought to be responsible for their elimination[33,34]. Loss of function mutation in *SLC22A2* gene has been significantly correlated with metformin disposition. In several studies, *SLC22A2* gene has been reported as highly polymorphic in nature[34-37]. Zolk *et al*[38] found that *SLC22A2* variant 808G > T (270Ala > Ser) significantly transforms the uptake of drugs. In healthy subjects, rs316019 (A270S) variant appeared responsible for decreased renal clearance of Metformin[30] while in a contradictory study a significant correlation of rs316019 was reported with increased metformin renal clearance[39]. Song *et al*[40] investigated the influence of rs201919874 (T199I) and rs145450955 (T201M) to the disposition of metformin in healthy individuals and reported that both were significantly associated with increased metformin plasma concentration and reduced renal clearance. A recent randomized cohort study performed in T2DM patients with one year follow-up demonstrated that efficacy of metformin was also influenced by *SLC22A2* variant, rs316019 (808G > T)[41].

Solute carrier family 22 member 3

Solute carrier family 22 member 3 *(SLC22A3)* gene encodes for OCT3 which is expressed in liver, kidney and placenta. In public SNP database (http://www.ncbi.nlm.nih.gov/SNP/) five non-synonymous variants (ssj0008476, rs8187717, rs8187725, rs12212246, rs9365165) of human *SLC22A3* gene were reported[42]. However, compared to OCT1 and OCT2, very few studies have reported about OCT3 variants and metformin therapeutics. In a pharmacologic study, Chen *et al*[43] studied the role of OCT3 variants ssj0008476 (T44M), rs8187725 (T400I) and V423F were found to be significantly associated with altered response to metformin action.

Solute carrier family 47 member 1

Solute carrier family 47 member 1 (*SLC47A1*) gene encodes the multidrug toxin extrusion receptor 1 expressed on apical domain of proximal and distal renal tubular cells and serves as an electro neutral organic cation/H^+ exchanger. Since genetic polymorphisms in *SLC47A1* associated with altered transport/excretion function might have great influence on metformin disposition, it is important to identify them in various ethnic populations and correlate in terms of therapeutic response. An intronic variant rs2289669 (G > A) in *SLC47A1* was demonstrated to reduce HbA1c level significantly in metformin users[44]. While in a DPP (Diabetes Preventation Programme) study, *SLC47A1* variant rs8065082 (C > T) was reported for lower diabetes incidence in individuals treated with metformin[45]. In a recent case control study the polymorphic effect of rs594709 in *SLC22A1* and rs2289669 in *SLC47A1* was evaluated in T2DM cases and no significant association was reported. The study concluded that carriers of allele "A" of rs594709 showed better efficacy for metformin[30]. In Chinese population, the *SLC47A1* variant rs2289669 (G > A) appeared to promote metformin efficacy by delaying its excretion mechanism[46].

Solute carrier family 47 member 2

Solute carrier family 47 member 2 (*SLC47A2*) encodes for multidrug toxin extrusion receptor 2 (MATE2), expressed in apical membrane proximal tubule cells. It facilitates the disposition of metformin from renal tubular cells into urine. Choi *et al*[47] characterized variants of *SLC47A2* to recognize their association with metformin. The study showed that homozygous individuals for rs12943590 (130G > A) of MATE2-K is significantly associated with poor plasma glucose control of metformin assessed by relative differences in HbA1C level.

SULFONYLUREAS

Sulfonylureas (SUs), insulin secretagogues are one of the most common classes of OADs being prescribed either alone or in combination since 1960s[8,48]. The second generation drugs *viz.* glimepiride, glibenclamide (glyburide), gliclazide and glipizide are most common representatives belonging to the group of SUs. The first-generation drugs *viz.* tolbutamide and chlorpropamide are no longer prescribed[10]. All SUs stimulate insulin secretion by binding to sulfonylurea receptor 1 (SUR1), a protein having 1581-amino acids. This interaction depolarizes the cell membrane of pancreatic beta cells by closing ATP-sensitive potassium (KATP) channels. Subsequent effect of depolarization leads to Ca^{2+} influx which trigger an enhanced insulin secretion from beta cells in glucose-independent manner[49]. KATP channel is a heterooctameric protein complex constructed by four inward-rectifier K^+ channel, *i.e.,* Kir6.2 (forming pore of KATP channel) coupled with SUR1, surrounding the pore[49]. In neonates, inactivating mutations in genes encoding Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*)

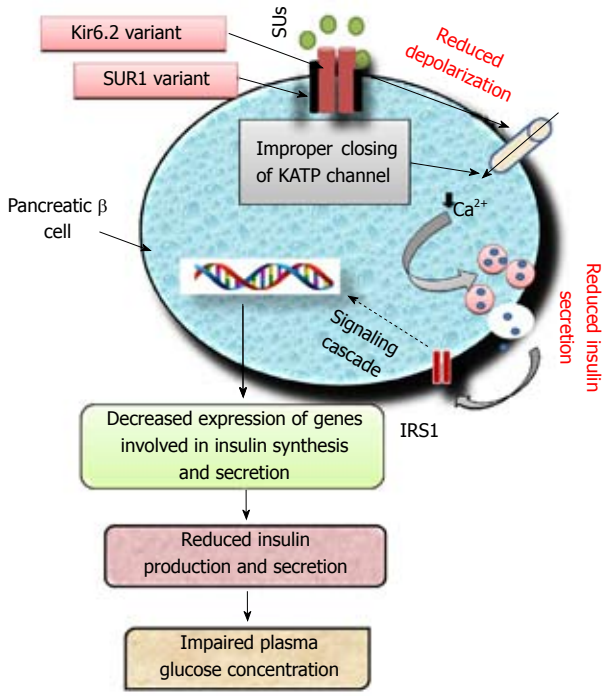

Figure 3 Schematic diagram showing the Kir6.2 and SUR1 variants affecting sulfonylurea efficacy. Pancreatic β cell membrane with SUR1/Kir6.2 variant leads to improper closing of KATP channel on binding with SUs. This subsequently leads to poor membrane depolarization and less influx of Ca^{2+} ions which will result in less and delayed insulin secretion. Hence, low level of insulin molecules will be available to bind with IRS1 and lead to an impaired signaling cascade resulting in poor management of glycemic condition. SUs: Sulfonylureas; SUR1: Sulfonylurea receptor 1; KATP: ATP-sensitive potassium channel; IRS1: Insulin receptor substrate 1; SUR 1: Sulfonylurea Receptor 1.

are responsible for T2DM, while activating mutations lead to hypoglycemia[50]. Polymorphisms in the genes *ABCC8, KCNJ11, CYP2C9, TCF7L2, NOS1AP* (nitric oxide synthase 1 adaptor protein) have been reported for altered response to SUs[51,52]. Impairment of Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) will lead to improper signaling cascade of insulin as shown in Figure 3.

GENES ASSOCIATED WITH SULFONYLUREA TREATMENT

Potassium inwardly-rectifying channel, subfamily J, member 11

ATP-sensitive potassium channel (KATP) is a transmembrane protein of pancreatic β-cells encoded by potassium inwardly-rectifying channel and subfamily J, member 11 (*KCNJ11).* Two hundred and nineteen SNPs have been reported for the KCNJ11 gene located on chromosome 11p15.1. Polymorphisms in *KCNJ11* have been reported for development of diabetes because of its key role in insulin secretion[53]. Only 6 SNPs *viz.* rs5210, rs5215, rs5218, rs5219, rs886288, rs2285676 have been reported to be associated with diabetes[54]. A study found that in T2DM patients the rs5210 variant located at 3' UTR of *KCNJ11* improves the clinical efficacy of gliclazide[52]. The most widely studied *KCNJ11* gene variant rs5219 (E23K) was significantly associated with the onset of T2DM in Asian Indian and Chinese populations[55,56]. However, studies performed on Caucasian individuals demonstrated for no significant differences in glycated hemoglobin[57,58]. Some studies have reported that diabetic patients having *KCNJ11* gene variants respond better to pharmacotherapy with SUs as compared to insulin[59-61].

ATP-binding cassette, subfamily C member 8

ATP-binding cassette, subfamily C member 8 (*ABCC8*) located at 11p15.1, encodes for SUR1 which modulate the activity of KATP channel[62]. Variants of *ABCC8* gene rs1799854 (C/T) and rs1801261 have been studied extensively and are reported for inconsistent association with T2DM[63-70]. *ABCC8* variant rs1799854 has been reported for significant association with sulfonylurea efficacy in terms of HbA1c level[57]. In one study, the genetic variants of *ABCC8* were reported for significant reduction in HbA1c concentration[71]. Activating mutation in the genes encoding SUR1 (*ABCC8*) and Kir6.2 (*KCNJ11*) may lead to altered signaling cascade of insulin secretagogues resulting in therapeutic failure of SUs. The Arg972 variant of insulin receptor substrate 1 is reported for an enhanced risk of secondary failure to SUs in T2DM patients[72]. A study carried out in Chinese T2DM patients with two months follow-up, demonstrated that Ser1369Ala variant of *ABCC8* is significantly associated with therapeutic success of gliclazide[73]. Carriers and non-carriers of SUR1-437A/T variant did not differ in insulin response stimulated by tolbutamide during OGT test[74].

Cytochrome P450 2C9

SUs *viz.* tolbutamide, glimperide, glipizide and glibenclamide are metabolized to active metabolites in the liver mainly by cytochrome P450 2C9 (*CYP2C9*)[75] which are ultimately excreted by the kidney[76]. It has been reported that *CYP2C9* variants were significantly associated with efficacy of SUs in diabetic patients[77]. Two variants of *CYP2C9* gene, *i.e.,* rs1057910 *(CYP2C9*3*) and rs1799853 *(CYP2C9*2*) have been significantly associated with missense amino acid polymorphisms resulting in decreased metabolism of SUs in healthy volunteers[74]. While in T2DM patients treated with SUs, *CYP2C9*3* variant was reported with an enhanced risk of severe hypoglycemia[78,79]. Certain T2DM patients with *CYP2C9* gene variants Ile359Leu and Arg144Cys were reported for 30%-80% reduction in renal clearance of glibenclamide suggesting lower doses of this antidiabetic drug to decrease the risk of hypoglycemia[51,75,77,80,81].

Transcription factor 7-like 2

Transcription factor 7-like 2 (*TCF7L2*) is encoded by *TCF7L2* gene which is actively involved in proliferation and differentiation of cells. It is required for secretion of glucose stimulated insulin from pancreatic β-cells. *TCF7L2* is a key transcription factor, which regulates glucose metabolism in insulin dependent manner. It serves as a chief regulator in coordinating the proinsulin

synthesis and its processing to produce mature insulin[82]. Hence, nucleotide variation in *TCF7L2* gene may lead to alteration in insulin secretion[31] resulting reduced insulin secretion will lead to hyperglycemia. *TCF7L2* gene is expressed in developing and mature pancreatic beta cells[83] and secretion of insulin is decreased in individuals having risk alleles[84-86]. Miyake *et al*[87] studied association of *TCF7L2* variants with susceptibility to T2DM in 4087 Japanese patients. They found that rs7903146, rs12255372 and rs11196205 were significantly associated with T2DM while rs290487 and rs11196218 were reported for no association. Polymorphisms in *TCF7L2* gene has been reported for strong association with T2DM affecting therapeutic response to SUs[88]. *TCF7L2* SNPs were reported to influence the risk of T2DM[89]. Polymorphisms in *TCF7L2*, rs12255372 and rs7903146 were reported for decreased response to sulfonylurea efficacy[88]. The SNPs rs12255372T and rs7903146T were represented to be significantly associated with enhanced expression of *TCF7L2* gene in beta cells, altering insulin release and predisposing individuals to T2DM[90,91].

TZDS

TZDs are insulin sensitizers, they promote uptake of glucose by tissue and skeletal muscles, down regulate glucose output from liver[92]. Rosiglitazone and pioglitazone are medical representatives of TZD group. The exact molecular mechanism of TZDs is far from clear. However, data indicates that TZDs primarily bind with the peroxisome proliferator-activated receptor γ (PPARγ) in adipose tissue and affect their metabolism. On binding with PPARγ, TZDs stimulate adipocytes differentiation[93] and decrease plasma glucose level in T2DM patients[94,95]. Several studies have reported that TZDs improve both glucose homeostasis and insulin cascading in T2DM cases[96-98], hence may prevent the progression from altered plasma glucose tolerance to T2DM development[99]. Numerous potential mechanisms are reported by which TZDs improve molecular action of insulin in both liver[98,100] and skeletal muscles[97,101]. These include reduced content of intra-hepatocellular and intra-myocellular triglycerides[98,102] and altered body composition[97,103]. It also decreases synthesis and/or action of proinflammatory cytokines[104,105]. TZDs upregulate expression of genes in adipocytes resulting in increased level of adiponectin in plasma circulation[106-108], with positive effects on insulin sensitivity[109] and reduced hyperglycemia. Some previous studies reported that use of rosiglitazone (a TZD drug) as compared to pioglitazone could cause severe side effects, the risk of myocardial infarction and also lead to death due to cardiovascular dysfunction[110,111]. Several gene variants have been identified for significant association with therapeutic outcome of TZDs. Adiponectin, resistin, leptin, TNF-α and PPARγ are commonly called adipocytokines which are key regulators of insulin resistance[112].

GENES ASSOCIATED WITH TZD TREATMENT

PPARγ

PPARγ belonging to the nuclear receptor family regulates metabolism of carbohydrates, regulates lipid homeostasis and adipocyte differentiation[113]. It is also a key mediator of insulin signaling[114]. In humans, TZDs bind to PPARγ with high specificity. At physiological pH PPARγ forms a dimer with retinoid X receptor (RXR). Binding of TZDs to the PPARγ-RXR complex stimulates a conformational change[115] which subsequently leads to the binding of the above heterodimer complex to the PPARγ response elements (PPRE) in the target genes[116]. It results in improved insulin sensitivity *via* glycolysis, lipogenesis, adipogenesis and increased glucose uptake and utilization[117]. Single nucleotide variations in *PPARγ* gene may affect the binding affinity with TZDs and its therapeutic efficacy (Figure 4). In *PPARγ* gene, loss-of-function mutations are significantly associated with insulin resistance and T2DM[118]. Multiple studies have reported that missense polymorphism Pro12Ala (CCA-to-GCA) in *PPARγ* gene is associated with decreased risk of T2DM development[119-121] and improved insulin sensitivity[122,123]. A pilot study performed on South Indian population, evaluated the effect of Pro12Ala variants on therapeutic success to pioglitazone, and reported a significant association with glycemic control[124]. T2DM cases with Pro12Ala variant of *PPARγ* gene, showed significant glycemic control [fasting plasma glucose (FPG) and HbA1c level] for rosiglitazone treatment as compared with carriers having wild-type genotype[125]. Zhang *et al*[126] demonstrated that in Chinese patients, amino acid variants Thr394Thr and Gly482Ser of peroxisome proliferator-activated receptor gamma coactivator 1-alpha were also significantly associated with efficacy of rosiglitazone.

Adipocytokines

Variants of adiponectin (*ADIPOQ)* gene have been reported for changes in FPG and level of HbA1c after 12 wk of rosiglitazone treatment. A study carried out by Liu *et al*[127] in T2DM Chinese patients demonstrated that sequence variation in leptin and TNF alpha gene interferes with therapeutic response to rosiglitazone. Nucleotide variants rs2241766 (45T/G) and rs266729 (-11377C/G) of *ADIPOQ* gene[128], rs1800629 (-308 G/A) of *TNF-α* and rs7799039 (-2548G/A) of leptin gene[127] were found to affect the rosiglitazone therapeutics and reverse insulin resistance in Chinese patients. In a pilot study, it was found that single nucleotide polymorphism at -420 (G/G) in resistin gene may serve as an independent predictor for down regulation of insulin resistance and hyperglycemia associated with pioglitazone therapeutics[129].

Cytochrome P450

Metabolism of rosiglitazone is mainly metabolized by

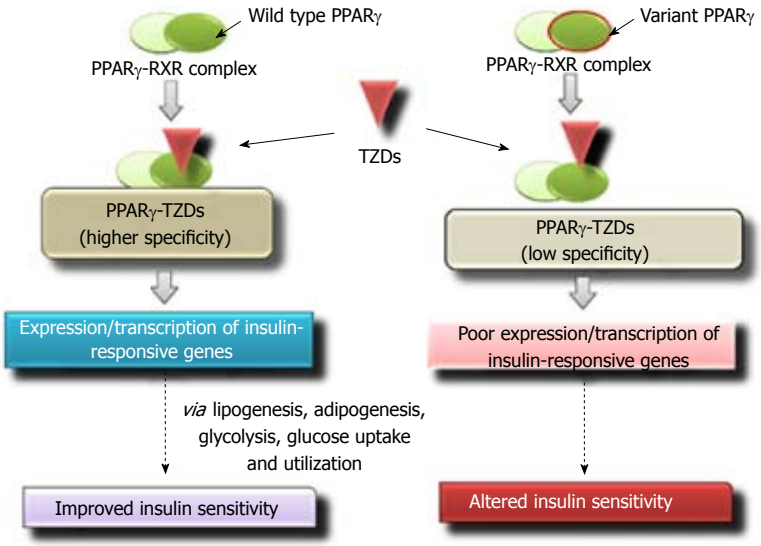

Figure 4 Schematic representations of peroxisome proliferator-activated receptor γ variants affecting the efficacy of thiazolidinediones. TZDs: Thiazolidinediones; PPARγ: Peroxisome proliferator-activated receptor γ.

CYP2C8 and *CYP2C9*[78] while biotransformation of pioglitazone is mainly metabolized by *CYP2C8* and *CYP3A4*[130]. Nucleotide polymorphisms in *CYP2C8* gene were significantly associated with impaired clearance of rosiglitazone. Polymorphisms in *CYP2C8*3* encoding for a reduced functioning of CYP2C8 enzyme, was reported for altered drug clearance[131]. Hence genetic variants of *CYP2C8* may contribute to the degree of TZD therapeutics.

MEGLITINIDE

Meglitinide, insulin secretagogues act by inhibiting KATP channel leading to promote insulin secretion. Molecular mechanism of both sulphonylureas and meglitinide are similar. Sulphonylureas and meglitinide inhibit the activity of KATP channel by binding at two different sites of the SUR1 subunit[132]. Meglitinides have shorter duration of action and more rapid onset as compared with SUs. Repaglinide (a benzoic acid derivative) and nateglinide (a derivative of d-phenylalanine) belonging to meglitinide stimulate early secretion of insulin. Due to their short action, a potential adverse effect of meglitinide is to induce hypoglycemia[133]. Repaglinide is 100% metabolized in liver and hence excreted mainly *via* bile. Genetic polymorphisms associated with response to meglitinide were mapped in *SLCO1B1, CYP2C8, CYP3A4, TCF7L2, SLC30A8, IGF2BP2, KCNJ11, KCNQ1, UCP2, NAMPT, MDR1, PAX4* and *NeuroD1*[78,134-139]. Out of these *SLCO1B1* is reported to facilitate the hepatic uptake of a drug repaglinide[140].

GENES ASSOCIATED WITH MEGLITINIDE TREATMENT

Solute Carrier Organic anion transporter family member 1B1

Solute Carrier Organic anion transporter family member 1B1 *(SLCO1B1)* gene, mainly expressed in basolateral membrane (hepatocytes) encodes for organic anion-transporting polypeptide 1B1 (OATP1B1). Genetic polymorphisms in *SLCO1B1* have been reported to exert significant influence on repaglinide pharmacokinetics with reduced exposure after administration of a single dose of repaglinide[141]. Genetic variant of *SLCOB1* gene (521T > C) markedly affected the pharmacokinetics of nateglinide[134]. Cellular uptake of various drugs is regulated by OATP1B1. Several studies have demonstrated the pivotal role of *SLCOB1* gene variants in pharmacokinetics of meglitinides[134,142-144]. Nateglinide is catabolized by *CYP2C9.* A study performed in Chinese male volunteers has demonstrated that genetic variants of *SLCOB1* (521T > C) and *CYP2C9* (*CYP2C9*3*) could affect the nateglinide efficacy[139].

OTHER GENES

CYP2C8 and *CYP3A4*, both are actively engaged in metabolism of repaglinide. Clinical studies demonstrate that individuals with *CYP2C8*3* variant have greater clearance of OADs as compared to wild-type genotype[78]. A Chinese population treated with repaglinide and genotyped for *KCNQ1* variants rs2237892 (C/T) and rs2237895 (C/A) were found to be associated with therapeutic efficacy of repaglinide[137]. Single nucleotide polymorphisms in *SLC30A8 viz.* Arg325Trp (rs13266634) and Arg325Gln (rs16889462) have been reported to be significantly associated with T2DM development and repaglinide efficacy[135]. *KCNJ11* SNP rs5219 (Lys23Glu) has been found to be associated with poor regulation of fasting/postprandial glucose and HbA1c levels in T2DM patients with "GA" or "AA" genotype in contrast with "GG". T2DM patients having "TT" genotype of *TCF7L2* gene rs290487 (C/T) demonstrated better efficacy for repaglinide treatment with respect to triglyceride, LDL and fasting insulin as compared to patients with "CC" or "CT" genotype[107].

DIPEPTIDYL PEPTIDASE 4

DPP-4 is involved in the degradation of two incretin

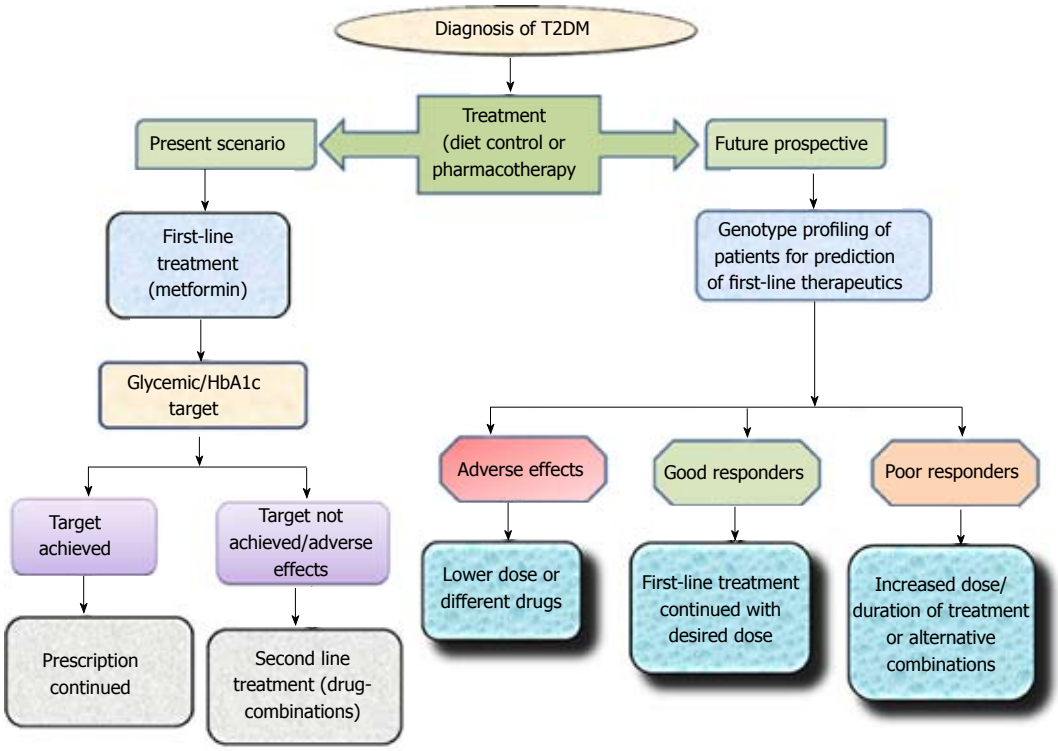

Figure 5 Clinical applications of pharmacogenetics in type 2 diabetes mellitus. T2DM: Type 2 diabetes mellitus; HbA1c: Glycated haemoglobin.

Table 1 Currently available antidiabetic drugs and their associated candidate genes involved in efficacy/toxicity

Class	Common medical representatives	Mechanism of action	Candidate genes involved in pharmacotherapy	Ref.
Biguanide	Metformin	AMP-kinase activation	*SLC22A1, SLC22A2, SLC22A3, SLC47A1, SLC47A2*	[28-39]
Sulfonylureas	Gliburide, gliclazide, Glimepiride, glipizide	Inhibition of KATP channel on plasma membrane of β-cells	*KCNJ11, ABCC8, CYP2C9, TCF7L2*	[8,10,48-91]
Thiazolidinediones	Pioglitazone, rosiglitazone	Activates PPAR-γ	*PPAR-γ, ADIPOQ, TNF-α, LEP, CYP2C8*	[92-131]
Meglitinides	Nateglinide, repaglinide	Inhibition of KATP channel on Plasma Membrane of β-cells	*SLCOB1, CYP2C8, KCNQ1, SLC30A8, KCNJ11, TCF7L2*	[78,106,132-144]
DPP-4 inhibitors	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	Inhibits DPP-4, Affect GLP-1 receptor pathway	Possibly *TCF7L2*	[145-148]
α-glucosidase inhibitors	Acarbose, miglitol, voglibose	Inhibits intestinal α-glucosidase	Yet to identify?	[10]
SGLT-2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin	Inhibits SGLT2 transporters in kidney	Yet to identify?	[10]
GLP-1 agonist	Exenatide, liraglutide	Activate GLP-1 receptor	Yet to identify?	[10]

DPP-4: Dipeptidyl peptidase-4; SGLT-2: Sodium glucose transporter-2; GLP-1: Glucagon like peptide-1; KATP: ATP-sensitive potassium channel; PPARγ: Peroxisome proliferator-activated receptor γ.

hormones *viz.* GLP-1 and gastric inhibitory polypeptide. These hormones bring about a glucose dependent stimulation of insulin release. These hormones are also responsible for reduction in circulating plasma glucose levels by interrupting glucagon secretion and subsequently improve beta cell sensitization by glucose[145]. DPP-4 inhibitors inhibit function of DPP-4 enzyme, thus reducing glucagon secretion. Sitagliptin, vildagliptin and saxagliptin are medical representatives of DPP4 inhibitors. Sitagliptin was the first DPP-4 inhibitor approved by Food and Drug Administration (FDA) in 2006[146]. Metabolism of saxagliptin (a DPP-4 inhibitor) is catalyzed by CYP3A4/A5 while sitagliptin is metabolized by CYP3A4 with minor contribution of CYP2C8[147]. Zimdahl *et al*[148] investigated the effect of *TCF7L2* variants for therapeutic efficacy of linagliptin, a DPP-4 inhibitor. Linagliptin was found to significantly improve glucose homeostasis in both cases with and without *TCF7L2* risk alleles for diabetes. Effects of genetic polymorphisms associated with DPP-4 inhibitors remain

to be investigated.

CONCLUSION

About 70 genetic loci have been identified to be associated with T2DM[149]. Pharmacogenetics, an expanding area of research provides a platform to understand and improve pharmacological treatment. Over the last decade, the number of available antidiabetic drugs has considerably increased. However, clinical treatment of T2DM patients has become more complex due to different degrees of therapeutic outcomes. Personalized differences during OADs therapeutics have been linked with numerous variants related to drug-transporters, drug-targets, drug catabolizing enzymes and T2DM risk genes (Table 1). Although inter-individual differences in respect to efficacy and toxicity of OADs are significantly associated with genetic makeup, it is clear that different degrees of response to antidiabetics cannot be predicted by studying the genetic differences alone. The role of genetic variations with respect to therapeutic outcomes must be further tested *via* clinical trials thus leading to a personalized pharmacotherapy. The present scenario and future prospect of Pharmacogenetic studies has been elaborated in Figure 5.

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ORIGINAL ARTICLE

Basic Study

Increased fecal viral content associated with obesity in mice

Hariom Yadav, Shalini Jain, Ravinder Nagpal, Francesco Marotta

Hariom Yadav, Department of Nutritional Biotechnology, National Agri-Food Biotechnology Institute, Mohali, Punjab 160071, India

Shalini Jain, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Ravinder Nagpal, Probiotics Research Laboratory, Juntendo University Graduate School of Medicine, Tokyo 1138421, Japan

Francesco Marotta, ReGenera Research group for Aging Intervention and Milano Medical, Gender Healthy Aging Unit by Genomics, 20122 Milano, Italy

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Correspondence to: Hariom Yadav, PhD, Scientist, Ramalingaswami Fellow, Department of Nutritional Biotechnology, National Agri-Food Biotechnology Institute, C-127, Industrial Area, Phase 8, Mohali, Punjab 160071, India. yadavhariom@gmail.com
Telephone: +91-301-496459
Fax: +91-301-4514800

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Abstract

AIM: To investigate the presence of total gut viral content in obese mice, and establish correlation with obesity associated metabolic measures and gut microbiome.

METHODS: Fresh fecal samples were collected from normal and obese (Leptin deficient: $Lep^{ob/ob}$) mice. Total viral DNA and RNA was isolated and quantified for establishing the correlation with metabolic measures and composition of gut bacterial communities.

RESULTS: In this report, we found that obese mice feces have higher viral contents in terms of total viral DNA and RNA ($P < 0.001$). Interestingly, these increased viral DNA and RNA content were tightly correlated with metabolic measures, *i.e.*, body weight, fat mass and fasting blood glucose. Total viral content were positively correlated with firmicutes ($R^2 > 0.6$), whilst negatively correlated with bacteroidetes and bifidobacteria.

CONCLUSION: This study suggests the strong corre-

lation of increased viral population into the gut of obese mice and opens new avenues to explore the role of gut virome in pathophysiology of obesity.

Key words: Obesity; Gut; Microbiome; Virome; DNA; RNA; Virus; Fat mass

Core tip: Gut microbiome is known for major constituents of bacterial population, and their association with obesity, but microbes like viruses are majorly neglected. Our investigation on the basis of hypothesis that viruses are an important part of microbial world, and found in substantial numbers into human gut, we investigated whether viral content have any correlation with obesity in mice models. Interestingly, we found that DNA and RNA viral fecal content was significantly increased in obese mice as compared to normal. This suggests that viral population may have role to regulate host metabolism and might impact obesity prevalence *via* alteration of gut microbiome composition. Our findings open a new area of research to explore the role of gut virome in obesity.

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INTRODUCTION

Obesity is reaching on higher epidemic around the globe[1]. This is because of lack of successful and effective strategies to prevent and treat this health ailment. The pathophysiology of obesity is highly complex, and involves various factors, *i.e.,* genetics, environment and life style[2]. Abdominal or central obesity (abdominal fat accumulation) is strongly correlated with increased incidence of insulin resistance and metabolic syndrome[3]. Abdominal fat is in close proximity with gastrointestinal tract, and have various gut-adipose communication through various gut hormones and adipokines[4]. Recently, role of gut microbiome in obesity pathophysiology have been well established and known to play significant role in obesity progression[5]. Human and rodent studies suggest that presence of gut microbiome increases the risk of weight gain and insulin resistance[6]. Various mechanisms have been proposed to explain the role of gut-microbiome on obesity progression, *i.e.,* increased energy harvesting capacity, low grade inflammation, endotoxemia and other metabolic interferences[7]. Recently, plethora of literature has been generated to explore the role of gut microbiome (especially bacterial community) in metabolic regulation. Therefore modulation of gut microbiome has been considered one of the important strategies to develop therapies against obesity and diabetes[7].

Most of the studies conducted for exploring the role of gut microbiome in obesity have been focused on bacterial communities and their correlation with host metabolism[8]. Role of viruses present into gut are not investigated in relation with obesity and their impact on host metabolism and associated gut bacterial microbiome. Viruses play a critical role in maintaining bacterial population in specific environment, *i.e.,* gut, where they establish a commensal relation with their partners[9]. Specific viral particles, especially bacteriophages might play an important role in maintaining certain bacterial strains of gut microbiome, that are correlated with obesity occurrence[6]. From our best knowledge, none of the studies investigated the direct link of gut virome with obesity. We hypothesize that changes in gut viral community (gut-virome), might play an important role in maintaining and colonizing gut bacterial species that impact host metabolism. Hence establishing the role of gut-viral community on influencing gut microbiome and host metabolism will open new avenues for development of therapeutic strategies against obesity *via* targeting gut virome. In this study, we investigated the correlation between gut-virome, obesity associated metabolic measures and gut bacterial communities in mice.

MATERIALS AND METHODS

Animals, sample collection and biochemical analysis

Lep$^{ob/ob}$ and C57J/B6 mice (male; age 6-8 wk old) were housed in a light controlled facility by maintaining 12 h light/dark cycle. Mice were maintained in identical conditions and fed with similar diet and water, adlibitum. Body weight was measured using a microscale balance (Cole-Parmer, IL, United States). Total fat mass was measured weighing all the major fat depots, *i.e.,* epididymal, perirenal, mesenteric, supra subscapular, anterior subcutaneous and posterior subcutaneous fat depots). Fasting (12-14 h) blood glucose was measured using Bayer Contour glucometer (Bayers Contour Diabetes Solutions, Thane, India). Fresh fecal samples were collected from each mouse by light abdominal squeezing and immediately stored in a sterile, DNase and RNase free vials at -80 ℃ till further use. All the animal protocols and procedures were approved by institutional animal ethics committee from University of Punjab and PGIMER, Chandigarh, India.

Viral DNA and RNA isolation and quantification

Fecal viral DNA and RNA was isolated using Qiagen viral DNA and RNA isolation kits following the manufacturer's instructions. DNA and RNA quality have been checked using Agilent 2100 Bioanalyzer. Viral DNA and RNA have been quantified using NanoDrop One

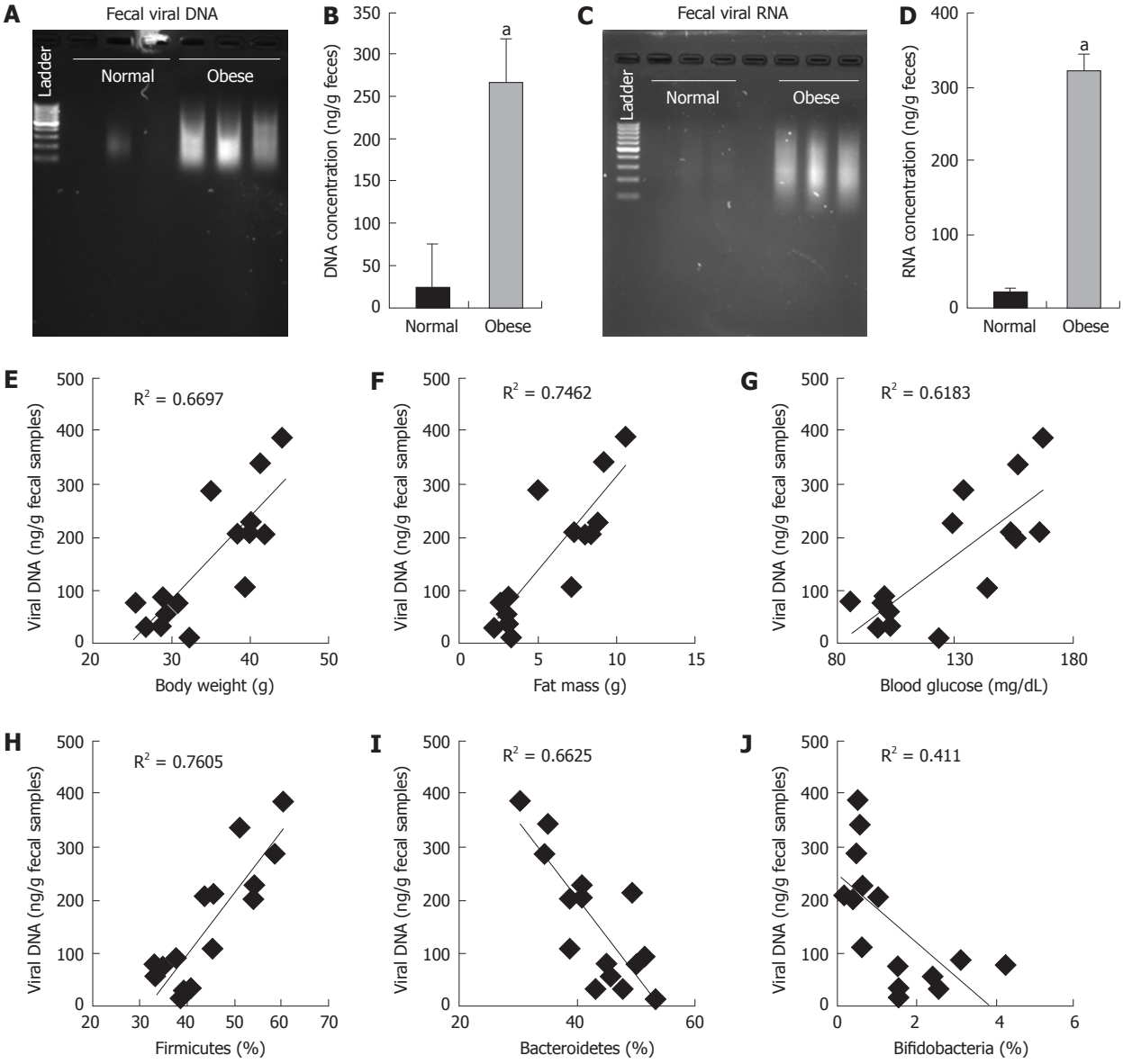

Figure 1 Fecal viral DNA and RNA content was significantly increased in obese mice and shown strong correlations with obesity associated measures and gut bacterial microbiome. A-D: Fecal viral DNA (A and B) and fecal viral RNA (C and D) content was found to be dramatically increased in obese animals; E-J: Viral DNA was positively correlated with body weight (E), fat mass (F), blood glucose (G) and firmicutes (H), whilst negatively correlated with bacteroidetes (I) and bifidobacteria (J). Values presented here are means (n = 7) and standard error of means. Values indicated with "a" are significantly different at the level of P < 0.001.

Table 1 Primers used for gut microbial community analysis

Gene Name	Primer sequence (5′ →3′)
Universal F (Total)	TCCTACGGGAGGCAGCAGT
Universal R (Total)	GACTACCAGGGTATCTAATCCTGTT
Bifidobacteria F	GCGTGCTTAACACATGCAAGTC
Bifidobacteria R	CACCCGTTTCCAGGAGCTATT
Bacteroidetes 934F	GGARCATGTGGTTTAATTCGATGAT
Bacteroidetes 1060R	AGCTGACGACAACCATGCAG
Firmicutes 934F	GGAGYATGTGGTTTAATTCGAAGCA
Firmicutes 1060R	AGCTGACGACAACCATGCAC

Spectrophotometer with fluorescent method (Thermo-Fisher Scientific, United States). Viral DNA and RNA quantity has been calculated nanogram per gram of fecal sample.

Bacterial DNA quantification

Mouse total fecal DNA was isolated from separate fecal pallets than viral DNA/RNA isolation, using DNeasy kit (Qiagen). Real time PCR was performed to measure the major obesity associated bacterial community, *i.e.,* Firmicutes, bacteroidetes and Bifidobacteria using microbe specific primers (Table 1). Results are presented here as percent of bacterial DNA abundance normalized by total bacterial DNA.

Statistical analysis

All the data expressed is mean and standard error of means. Statistical significance among the groups was calculated using two-tailed *t* test and/or one way analysis of variance, that followed by *post-hoc* tests.

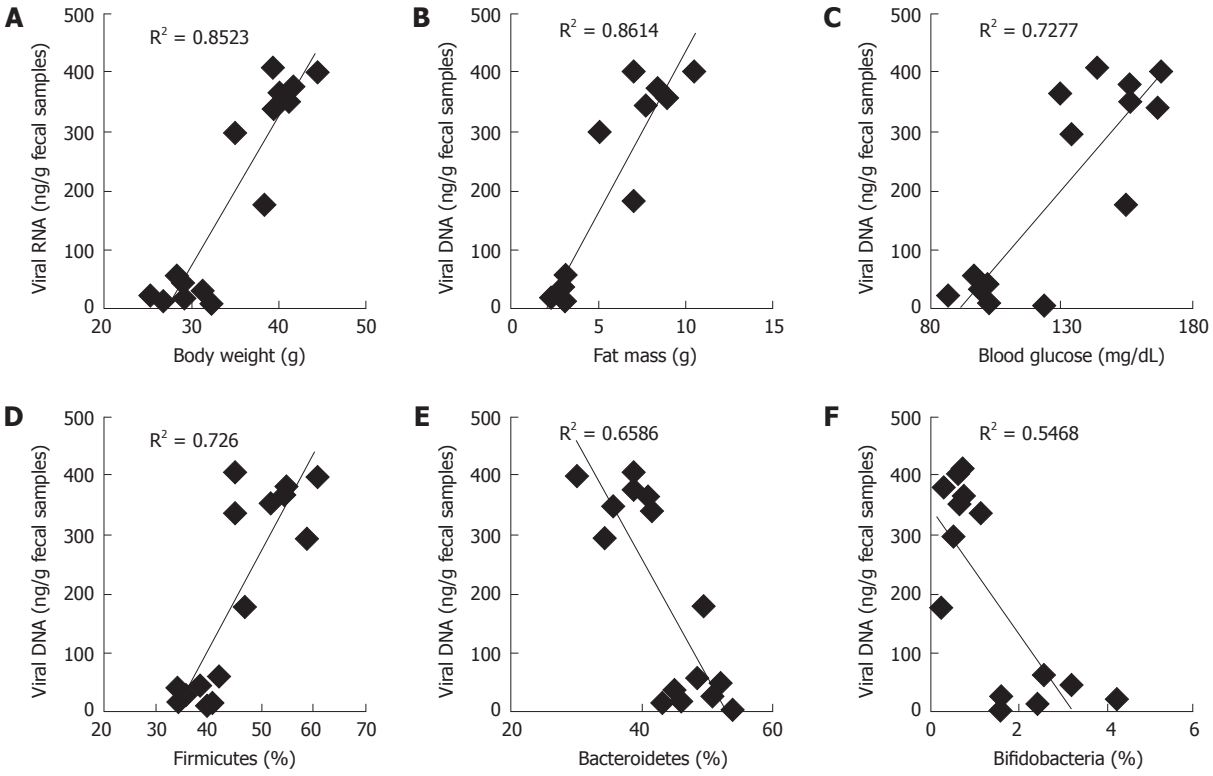

Figure 2 Fecal viral RNA content was significantly correlated with obesity associated measures and gut bacterial microbiome. A-F: Fecal viral RNA content was positively correlated with body weight (A), fat mass (B), blood glucose (C) and firmicutes (D), whilst negatively correlated with bacteroidetes (E) and bifidobacteria (F). Values presented here are means (n = 7) and standard error of means.

Data with less than 0.05 *P*-values considered statistically significance.

RESULTS

Microbiome studies clearly suggest that we are surrounded by microbes, in which viruses makes a significant numbers. Around 10^{31} viral particles have been estimated on earth, and human feces consist around 10^9 viral particles/gram[10-12]. Mammalian virome collectively called for viruses that infect eukaryotic cells (eukaryotic virome), bacterial cells (bacterial virome), archeal cells (archeal virome) and virus derived genetic elements in host chromosomes that can change host-gene expression, express proteins, or even generate infectious virus (prophages, endogenous retroviruses, endogenous viral elements)[13]. Viral infections have been associated with prevalence of obesity in animals and humans, and termed as infectobesity[14]. Considering the technological limitations for sequencing and analyzing datasets for viral communities, studies of virome has been lagged behind than bacterial microbiome. In present study, we analyzed total fecal viral content in normal *vs* obese (leptin deficient $Lep^{ob/ob}$) mice and correlated with obesity related measures. Interestingly, we found that fecal viral DNA and RNA in obese samples was significantly higher than normal mice (Figures 1 and 2), suggesting that total DNA and RNA viral communities have been significantly increased in obese mice. Although, our studies completely lack the types of viruses enriched in obese mice gut as compared to normal, but these very interesting observations indicate that total load of viruses have been increased in obese gut. Therefore, these results provide a strong basis to further explore the role of gut virome in obesity.

DISCUSSION

We have observed that fecal DNA and RNA viral population positively correlated with firmicutes bacterial communities, which is known to be associated with increased obesity[5]. While viral contents were negatively correlated with bacteroidetes and bifidobacteria, that are known to be associated with lean-ness[5]. These results can be speculated in a way, that gut virome (especially bacteriophages) might have interaction with gut bacterial microbiome to modulate the bacterial species abundance in obese *vs* normal mice. Although, these studies gives us an intrigued and important preliminary information about the abundance of DNA and RNA viruses in obese and normal mice, but still detailed analysis to find out the types of viruses and their functionality remains completely unknown. Therefore, further studies to explore the types of viruses that are associated with increased viral DNA and RNA contents in normal *vs* obese mice are highly warranted.

Viruses are highly mutagenic and carries individual variations in gut viral communities have been described

earlier[9]. Viral proteins can interact with host cells and can induce biological response, *i.e.,* inflammation, receptor based cell signaling or gene expression, to modulate adipose tissue biology[15]. Hence, the results of this study also indicate that increased viral population might be contributing to release of higher amount of certain viral proteins that can interact directly with host cells to modulate metabolism and cause obesity. Therefore it will be very important to establish how these viral species and their end products (*i.e.,* proteins) are playing role in modulation of gut bacterial communities, as well as their impact on host metabolism.

COMMENTS

Background

Viruses have been known to infection host, bacterial and other broad array of organisms. Gut bacterial microbiome have been known to play critical role in obesity pathology, but the role of gut virome have not been explored.

Research frontiers

The facts that viruses interacts with host cells as well as infects bacterial cells to control bacterial growth, studying virome compositions is one of the important aspects in the microbiome biology and its impact of health. Role of gut virome in obesity and gut bacterial microbiome modulation will open new frontiers of investigations.

Innovations and breakthroughs

The authors first time have reported that total viral population have been changed in obesity mice and correlated with metabolic and gut bacterial microbiome.

Applications

This study further open new avenues to find different types of viral populations in obese *vs* normal population and can develop them as a new drug targets or biomarkers.

Terminology

Gut virome is considered as collective viral community present in fecal samples.

Peer-review

In the current study, the authors explored the association between fecal viral content and obesity in mice. The results are significant as the fecal viral DNA and RNA content found to be elevated in obese mice model.

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