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Research Article

Common Hub Genes and Drug Candidates for Diabetic Kidney Disease and Non-Alcoholic Fatty Liver Disease: A Comprehensive Bioinformatic Study

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ABSTRACT

Diabetes mellitus (DM) is one of the most prevalent diseases responsible for worldwide morbidity and mortality. The kidney and liver are the most commonly affected organs resulting in diabetic kidney disease (DKD) and non-alcoholic fatty liver disease (NAFLD). However, pathophysiological mechanisms that may be common to both DKD and NAFLD have not been elaborated despite having a common underlying cause. This study aimed to identify the hub genes that are common to both DKD and NAFLD and explore the potential drugs for their treatment. Gene expression datasets for DKD and NAFLD from the gene expression omnibus database were analyzed to identify differentially expressed genes (DEGs). A functional enrichment analysis of the DEGs was done to reveal pathways important in the etiology of DKD and NAFLD. Protein-protein interaction (PPI) network was constructed and hub genes were identified. The hub genes were further analyzed to identify potentially viable drug candidates after screening. A total of 89 DEGs were found to be common between DKD and NAFLD. Functional enrichment of said DEGs found Ppar, FoxO signaling and hepatocellular carcinoma pathways to be most prevalent in DKD and NAFLD. From the PPI network, 32 common hub genes were identified. The hub genes were analyzed for interacting drugs. Finally, 9 drugs were identified as potential candidates for the treatment of both diseases. The hub genes identified can provide new insights into the common etiology of DKD and NAFLD. The potentially viable drugs may be repurposed for the treatment of both DKD and NAFLD.

Introduction

Diabetes mellitus (DM) is one of the four most prevalent non-communicable diseases responsible for morbidity and mortality worldwide.[1] Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[2] International Diabetes Federation has revealed in their Diabetes Atlas of 2021 that 10.5% of the global adult population aged between 20 to 79 years have diabetes[3]. The foundation has projected that by 2045, 1 in 8 adults, i.e., 783 million people will be living with this disease.[3] Besides the pancreas, kidney and liver are the organs most affected by the presence of DM in the body.[4,5] Diabetic kidney disease (DKD) and non-alcoholic fatty liver disease (NAFLD) are the most prevalent complications that occur in patients with DM, with cardiomyopathy and retinopathy being the other complications.[4,5] The kidney is affected in nearly 20 to 40% of cases in patients with DM which may progress to severe loss of kidney function with reduced glomerular filtration rate leading to kidney failure and end-stage renal disease.[6]

In patients with DM, there is a 45 to 75% prevalence of NAFLD since obesity and metabolic syndrome induce both the conditions in the body.[7-9] Therefore DM and NAFLD are correlated in a complex relationship.[9] Diabetes is known to increase the risk of NALFD to the more severe form of inflammatory non-alcoholic steatohepatitis (NASH) as well as hepatocellular carcinoma.[9]

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Current management practices of both DKD and NAFLD rely less on their mechanistic pathway intervention and more on controlling diabetes mellitus by lowering blood sugar levels. Sodium-glucose transport protein 2 (SGLT2) inhibitors are the prevalent therapeutics used to bring blood sugar levels under control by targeting the kidney, while drugs like metformin (N, N-dimethylbiguanide) are used to reduce the absorption of glucose from the intestines, simultaneously lower liver glucose production, and improve insulin sensitivity.[10,11] It has been shown that about 20% of patients inevitably develop DKD even if their blood glucose is well controlled.[12] SGLT2 inhibitors like canagliflozin, empaglifozin, and dapaglifozin reduce the urine albumin to creatinine ratio (UACR, a measure of kidney health and function) by 30%, reduce the risk of worsening nephropathy, albuminaria by 39% and 38% respectively.[13] However, these drugs are only partially effective, as even with the use of established RAS and SGLT2 inhibitors, 5.27% of patients still progressed to end-stage kidney disease.[14] While these drugs provide relief in the initial stages of DM, however, chronic hyperglycemia inevitably causes damage to the kidney, leading to DKD.

Despite diabetic patients having an incidence of 55% NAFLD, there is no approved medication for NAFLD till date.[15] Biguanides like metformin is the most commonly prescribed drug while other drugs include thiazolidinediones, such as pioglitazone and rosiglitazone, glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors. However, metformin does not show significant improvement in liver histology with respect to liver fibrosis in NAFLD, while the other classes of drugs show some improvement in liver inflammation and steatosis but not for fibrosis.[15]

Thus there is a need to comprehend the pathophysiological mechanism of DKD and NAFLD in order to find out driver genes and to develop therapeutic interventions against these targets; preferably such therapeutics that may be able to target both diseases simultaneously.

Therefore, the aim of this study was threefold. First, was to identify the differentially expressed genes (DEGs) from datasets of DKD and NAFLD and the molecular pathways commonly involved in both these diseases. The Second was to identify the hub genes that may be common to both the diseases as well as those hub genes unique to each disease so as to delineate the driver genes in the etiology of the two diseases. Identification of hub genes would reveal the genes that are important in the development and/or progression of DKD and NAFLD as a consequence of DM. Since the commonly used drugs for the management of DKD and NAFLD are only partially effective, it is essential to identify drug targets or leads that can be direct interventions for DKD and NAFLD. Therefore, the third aim of this study was to identify potential drug candidates which may be direct interventions for DKD and NAFLD by targeting commonly involved driver genes or by targeting multiple driver genes unique to each of the diseases. The intention of this study is to identify drugs commonly available in the market based on their potential interaction with these hub genes and screened for their absorption, distribution, metabolism, excretion and toxicity (ADMET) properties and drug-likeness so as to act as candidate therapeutics which may be developed further, thus expanding treatment repertoire for DKD and NAFLD, and decreasing reliance solely on diabetes controlling drugs.

Materials And Methods

Dataset Analysis

Two publicly available gene expression datasets, GSE 642 for diabetic kidney disease and GSE 39752 for diabetic liver disease along with their respective control tissues, from the gene expression omnibus (GEO) database were considered. GEO2R, a free web tool from the GEO database was used to analyze the two datasets separately, to determine the differentially expressed gene(s) (DEGs) between the diseased condition and control samples for each of the datasets. According to the metadata of the datasets, the control and diabetic condition samples were named for each of the datasets, and the 'reanalyze' feature was used after selecting the 'Benjamini & Hochberg false discovery rate' for multiple testing correction, 'Force normalization' and 'Limma precision weights' parameters in the "Options" tab and leaving the rest of the parameters to the default values. The DEGs identified were downloaded as CSV tables and further analyses were done with same. The significant DEGs identified from the downloaded tables were those whose adjusted *p-value* < 0.05 and their log 2 fold change (LogFC) values were either ≥ 0.5 or ≤ -0.5.

Common and Unique DEGs

The significant DEGs identified from the diabetic kidney disease and diabetic liver disease datasets were analyzed by the 'Venn' function of the free functional enrichment analysis tool (FunRich) version 3.1.4[16] to determine any DEGs which were common to both the disease conditions and those which were unique to each of the datasets. The DEGs common to both diabetic kidney and liver disease were designated as "Common DEGs" and those unique to the two disease conditions were designated as "Kidney DEGs" and "Liver DEGs", respectively. Further analyses were carried with the common DEGs, kidney DEGs and liver DEGs.

Protein-protein interaction network construction and identification of hub genes

Search tool for the retrieval of interacting genes/proteins (STRING) version 12.0 was utilized to construct separate PPI networks with the common DEGs, kidney DEGs and liver DEGs, respectively, with default settings. The predicted networks were exported to Cytoscape software (version

3.10.1) for the identification of hub genes. The Cytohubba plug-in was used to determine the hub genes for each of the imported PPI networks corresponding to common DEGs, kidney DEGs and liver DEGs, respectively. For each PPI network, the top 10 hub genes were identified for all the 11 topological analysis methods viz. maximal clique centrality (MCC), maximum neighborhood component (MNC), density of maximum neighborhood component (DMNC), degree, edge percolated component (EPC), bottleneck, eccentricity, closeness, radiality, betweenness, and stress, so as to obtain the maximum number of genes having relevance in the networks. The non-overlapping DEGs were collated to attain a consolidated list of hub genes for each network. Further analyses were carried out with the consolidated hub genes for the common DEGs, kidney DEGs and liver DEGs, respectively.

Enrichment analysis of the consolidated hub genes

The consolidated hub genes for the common DEGs, kidney DEGs and liver DEGs were analyzed using Enrichr- the gene set enrichment analysis web server[17-19] with default settings. The gene ontology (GO) analyses for 'Biological Process' were considered along with the enrichment of pathways from the Kyoto encyclopedia of genes and genomes (KEGG) having adjusted *p-value* < 0.05.

Drug-gene interaction and identification of potential therapeutic candidates

The consolidated hub genes identified from the common DEGs, kidney DEGs and liver DEGs were uploaded to the drug gene interaction database (DGIdb) separately to determine the predicted drug interactions. The 'Approved drugs' filter was selected to include only clinically approved drugs in the results. The drug lists were downloaded as CSV files and subjected to further analysis.

The drugs interacting with the hub genes from common DEGs, kidney DEGs and liver DEGs were analyzed by the 'Venn' function of the FunRich tool to identify the drugs typically to the hub genes for common DEGs as well as the hub genes for kidney DEGs and liver DEGs. Such a combination of interacting drugs would help to provide comprehensive coverage of all the possible drugs that interact with multiple DEGs in both disease conditions.

The two sets of interacting drugs were screened individually for ADMET properties and drug-likeness using the SwissADME web tool.[20]

RESULTS

Analysis of the Datasets for Diabetic Kidney Disease and Diabetic Liver Disease

Analysis of the datasets GSE 642 for diabetic kidney disease and GSE 39752 for diabetic liver disease identified 2567 and 1842 total DEGs having adjusted *p-value* < 0.05. Of the total DEGs, 1173 were upregulated and 1040 were downregulated in the dataset GSE 642 for diabetic kidney disease while 306 DEGs were upregulated and 367 DEGs were downregulated in the dataset GSE 39752 for diabetic liver disease (NAFLD).

Identification of Common and Unique DEGs for the Datasets GSE 642 and GSE 39752

'Venn' function of FunRich tool identified 89 genes to be common between the two datasets, designated as "Common DEGs" (Fig.1) while 1936 and 488 DEGs were unique to DKD and NAFLD; the latter two have been designated as "Kidney DEGs" and "Liver DEGs", respectively.

Identification of Hub Genes

Hub genes are genes that have many interactions with other genes.[21,22] They signify the differentially expressed genes most likely to be crucially involved in either the induction of the concerned disease pathophysiology or in the establishment or progression of the disease in the relevant organs.[22,23] Therefore, for the identification of hub genes among the common DEGs, kidney DEGs and liver DEGs, an initial PPI network was constructed for each, utilizing the STRING web tool. Once the PPI networks were constructed they were separately analyzed by the Cytohubba plug-in of the Cytoscape software. Collating the non-overlapping genes identified with the 11 analysis methods mentioned previously by the Cytohubba plug-in, there were 32 consolidated hub genes for the common DEGs (Table 1), 45 consolidated hub genes for the kidney DEGs and 46 consolidated hub genes for the liver DEGs. From Table 1 it can be seen that of the hub genes from the common DEGs, 4 are upregulated and 15 are downregulated while the rest 13 hub genes show contrary regulation.

Functional Enrichment Analyses of the DEGs

The common DEGs as well as the kidney DEGs and liver DEGs were analyzed separately by the Enrichr tool to reveal the KEGG pathways and GO terms enriched. The top 5 KEGG pathways enriched as well as the top 5 GO terms enriched related to 'Biological process' based on adjusted *p-value*, in each of the common DEGs, kidney DEGs and liver DEGs have been shown in Table 2. PPAR

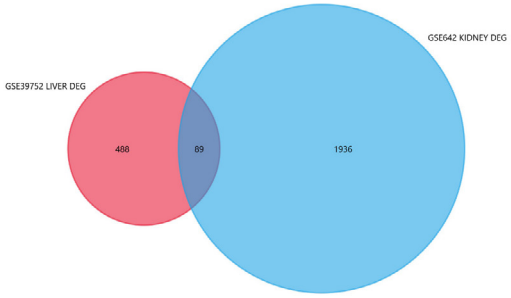

Fig. 1: Venn diagram showing the number of common DEGs, kidney DEGs and liver DEGs

Table 1: Hub genes from the common degs

S. No.	*Gene symbol*	*Gene name*
1	Cyp7b1	Cytochrome p450, family 7, subfamily b, polypeptide 1
2	Notch1	Notch 1
3	Cd36	Cd36 antigen
4	Ppargc1a	Peroxisome proliferative activated receptor, gamma, coactivator 1 alpha
5	Me1	Malic enzyme 1, nadp(+)-dependent, cytosolic
6	Hsd3b2	Hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2
7	Egfr	Epidermal growth factor receptor
8	Gss	Glutathione synthetase
9	Scp2	Sterol carrier protein 2, liver
10	Cbr1	Carbonyl reductase 1
11	Plk2	Polo-like kinase 2
12	Ppp2r5a	Protein phosphatase 2, regulatory subunit b', alpha
13	Spp1	Secreted phosphoprotein 1
14	Acsl1	Acyl-coa synthetase long-chain family member 1
15	Acaa1b	Acetyl-coenzyme a acyltransferase 1b
16	Mmp14	Matrix metallopeptidase 14 (membrane-inserted)
17	Tfrc	Transferrin receptor
18	Pck1	Phosphoenolpyruvate carboxykinase 1, cytosolic
19	Srxn1	Sulfiredoxin 1 homolog (s. Cerevisiae)
20	Ppara	Peroxisome proliferator activated receptor alpha
21	Serpine2	Serine (or cysteine) peptidase inhibitor, clade e, member 2
22	Gsto1	Glutathione s-transferase omega 1
23	Gadd45g	Growth arrest and dna-damage-inducible 45 gamma
24	Gck	Glucokinase
25	Sgk1	Serum/glucocorticoid regulated kinase 1
26	Cyp4a10	Cytochrome p450, family 4, subfamily a, polypeptide 10
27	Pik3r1	Phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)
28	Gsta4	Glutathione s-transferase, alpha 4
29	Btg2	B cell translocation gene 2, anti-proliferative
30	Nqo1	Nad(p)h dehydrogenase, quinone 1
31	Rnd2	Rho family gtpase 2
32	Gadd45b	Growth arrest and dna-damage-inducible 45 beta

signaling, hepatocellular carcinoma, FoxO signaling, adipocytokine signaling pathways and metabolism of xenobiotics by cytochrome P450 were most enriched in the Common DEGs. Pathways in cancer, protein processing in the endoplasmic reticulum, Alzheimer's disease and thyroid hormone signaling pathways were enriched in kidney DEGs. Glycerolipid metabolism, fatty acid elongation, fat digestion and absorption and peroxisome pathways were enriched in liver DEGs, among others. GO terms- intracellular glucose homeostasis, response to endoplasmic reticulum stress and monocarboxylic acid transport were predominantly enriched in common DEGs, kidney DEGs and liver DEGs, respectively.

The consolidated hub genes for the common DEGs, kidney DEGs and liver DEGs were also analyzed by the Enrichr tool to reveal the KEGG pathways and GO biological process (GO-BP) that were most enriched. The top 5 pathways based on adjusted *p-value* have been shown in Table 3. FoxO signaling pathway, PPAR signaling pathway, hepatocellular carcinoma, adipocytokine signaling pathway and insulin resistance were the top five KEGG pathways to be enriched in the hub genes from the common DEGs. Prostate cancer, pathways in cancer, colorectal cancer, microRNAs in cancer and thyroid hormone signaling pathways were enriched in the hub genes from the kidney DEGs. The top five KEGG pathways enriched in the hub genes from the liver DEGs were HIF-1 signaling pathway, AMPK signaling pathway, pathways in cancer, non-alcoholic fatty liver disease and prolactin signaling pathway.

Intracellular glucose homeostasis, regulation of cold-induced thermogenesis were the top GO-BP terms enriched for the hub genes from the common DEGs. Regulation of keratinocyte migration and positive regulation of phosphoprotein phosphatase activity were the top GO-BP terms enriched in hub genes from the kidney DEGs. The top GO-BP terms enriched in hub genes from the liver DEGs were lipid biosynthetic process and fatty acid metabolic process. These enrichment data show the prevalent types of molecular pathways that the hub genes are involved in, with respect to their function in the cells and the biological processes that are involved in the etiology and establishment of diabetic disease conditions.

Predicted drug gene interaction

The DGIdb was utilized to predict predicted drug gene interaction (DGI) for the hub genes for common DEGs, kidney DEGs and liver DEGs. The data from DGIdb has shown 333, 305 and 184 approved drugs to potentially interact with the three sets of hub genes from common, kidney and liver DEGs, respectively. The 'Venn' function of the FunRich tool identified that 23 drugs were commonly interacting with multiple genes of all three sets hub genes thus indicating that drugs were capable of interacting with hub genes common to both the diseases. 23 drugs typically interacted with multiple hub genes unique to both kidney and liver diseases but not the common set of hub genes.

Table 2: Top 5 terms enriched in kegg pathways and go biological processes for common DEGS, kidney DEGS and liver DEGS sorted by adjusted *p-value*

KEGG 2021 Term	*Adjusted p-value*	*GO-BP Term*	*Adjusted p-value*
Common DEGS			
PPAR signaling pathway	7.37E-06	Regulation of cell population proliferation (Go:0042127)	0.010808
Hepatocellular carcinoma	7.98E-05	Intracellular glucose homeostasis (Go:0001678)	0.010808
FoxO signaling pathway	1.24E-04	Positive regulation of biosynthetic process (Go:0009891)	0.010808
Adipocytokine signaling pathway	6.71E-04	Regulation of cold-induced thermogenesis (Go:0120161)	0.010808
Metabolism of xenobiotics by cytochrome P450	7.50E-04	Positive regulation of fatty acid metabolic process (Go:0045923)	0.010808
Kidney DEGS			
Pathways in cancer	6.13E-06	Response to endoplasmic reticulum stress (Go:0034976)	5.21E-06
Protein processing in endoplasmic reticulum	1.22E-04	Positive regulation of dna-templated transcription (Go:0045893)	0.001925
Alzheimer disease	1.35E-04	Purine ribonucleoside triphosphate metabolic process (Go:0009205)	0.005168
Thyroid hormone signaling pathway	2.46E-04	Positive regulation of transcription by rna polymerase ii (Go:0045944)	0.009068
Spinocerebellar ataxia	3.02E-04	Negative regulation of apoptotic signaling pathway (Go:2001234)	0.015746
Liver DEGS			
Glycerolipid metabolism	0.003772	Monocarboxylic acid transport (Go:0015718)	0.001607
Fatty acid elongation	0.047094	Organonitrogen compound biosynthetic process (Go:1901566)	0.001607
Fat digestion and absorption	0.047094	Lipid transport (Go:0006869)	0.007602
Peroxisome	0.052239	Positive regulation of cold-induced thermogenesis (Go:0120162)	0.009231
p53 signaling pathway	0.097229	Fatty acid biosynthetic process (Go:0006633)	0.009231

Identification of Potential Therapeutic Drugs

Screening of all the drugs common to all the three sets of hub genes as well as those drugs common to hub genes from kidney and liver DEGs through the SwissADME web tool led to the identification of 9 drugs as viable lead candidates in terms of ADMET properties and drug-likeness (Table 4). These drugs may be further developed or repurposed as a consolidated panel with multiple targets for the treatment of both diabetic kidney disease and diabetic liver disease as a whole instead of having different panels of drugs for these parallelly occurring diseases. The target hub genes for these drugs may serve as pivotal points of intervention in the development and progress of kidney and liver disease as a consequence of diabetes.

Discussion

This study revealed 89 DEGs that are common to both DKD and diabetic liver disease (NAFLD) in datasets with DM (Fig. 1). Therefore, PPI networks were constructed from the DEGs to predict the interaction of these common DEGs among themselves. The network so constructed facilitated in identifying hub genes in these commonly occurring DEGs from both diseases. Cytohubba plug-in helped to identify 32 such hub genes from the common DEGs. Of these, 4 are upregulated and 15 are downregulated while the rest 13 showed contrary regulation (Table 1).

Enrichment analysis helps in acquiring mechanistic insights from gene lists generated by genomics experiments, and identifies biological pathways involved in the experimental conditions, more than would be expected by chance.[24] Enrichment analysis of these hub genes revealed FoxO, Ppar and hepatocellular carcinoma signaling pathways as the most enriched along with the intracellular glucose homeostasis process, after adjusting for multiple testing correction Table 3. The pathways and processes enriched have a high probability of being predominantly involved in the pathophysiology of both DKD and NAFLD. Prevalence of these signaling pathways indicates that these mechanisms, particularly those involved in carcinoma development (either biomarkers or initial stage initiators) are commonly involved in both DKD and NAFLD and may be targeted for further study.

The hub genes Pck1, Ppara and CD36 have been studied to be deregulated and found to be involved in hepatocellular

Table 3: Top 5 terms enriched in kegg pathways and go biological processes for hub genes from common DEGS, kidney DEGS and liver DEGS sorted by adjusted *p-value*

KEGG 2021 term	*Adjusted p-value*	*GO-BP Term*	*Adjusted p-value*
Common DEGS			
FoxO signaling pathway	1.41E-07	Intracellular glucose homeostasis (Go:0001678)	4.89E-04
PPAR signaling pathway	1.41E-07	Regulation of cold-induced thermogenesis (Go:0120161)	0.001275
Hepatocellular carcinoma	3.94E-07	Regulation of protein localization to plasma membrane (Go:1903076)	0.002004
Adipocytokine signaling pathway	3.18E-06	Glucose homeostasis (Go:0042593)	0.002095
Insulin resistance	2.41E-05	Steroid metabolic process (Go:0008202)	0.002095
Kidney DEGS			
Prostate cancer	1.44E-05	Regulation of keratinocyte migration (Go:0051547)	0.001511
Pathways in cancer	2.24E-05	Positive regulation of phosphoprotein phosphatase activity (Go:0032516)	0.003696
Colorectal cancer	8.42E-05	Positive regulation of phosphatase activity (Go:0010922)	0.00462
MicroRNAs in cancer	2.56E-04	Regulation of cell size (Go:0008361)	0.00515
Thyroid hormone signaling pathway	2.56E-04	Negative regulation of cell size (Go:0045792)	0.00804
Liver DEGS			
HIF-1 signaling pathway	0.012268	Lipid biosynthetic process (Go:0008610)	1.38E-05
AMPK signaling pathway	0.012268	Fatty acid metabolic process (Go:0006631)	0.002632
Pathways in cancer	0.012268	Regulation of mirna transcription (Go:1902893)	0.002632
Non-alcoholic fatty liver disease	0.015793	Fatty acid biosynthetic process (Go:0006633)	0.002632
PPAR signaling pathway	0.015793	Monocarboxylic acid biosynthetic process (Go:0072330)	0.002632

Table 4: Viable drug candidates showing drug- gene interactions

S. No.	*Drug*	*Gene*	*Match type*	*Interaction*
1	Alpelisib	Pik3r1, Sgk1	Definite	Inhibitor for Pik3r1
2	Fenofibrate	Ppara	Definite	Agonist
3	Clofibrate	Ppara	Definite	Agonist
4	Bortezomib	Notch1	Definite	-
5	Ribociclib	Notch1	Definite	-
6	Triamterene	Tp53, Esr1	Definite	-
7	Atenolol	Pth, Bax	Definite	-
8	Phenobarbital	Pth, Bax	Definite	-
9	Fluvastatin	Apoe, Srebf1	Definite	-

carcinoma and NAFLD.[25-27] A fact to be highlighted is that these genes are involved in pathways of hepatocellular carcinoma which might indicate that even at early stages of diabetic liver disease, such genes and therefore such pathways become deregulated. Therefore, they may be necessarily further studied as targets of therapeutic intervention. Regulation of Notch1 hub gene has also been found to ameliorate proteinuria in DKD.[28] Polymorphism in the hub gene Ppargc1a has been linked to higher risk of DKD, particularly in Asian patients.[29]

The study also revealed 46 hub genes unique to the kidney DEGs and 49 hub genes unique to the liver DEGs. enrichment analysis of the unique hub genes for kidney DEGs has shown several cancer pathways including prostate, colorectal cancer, and thyroid hormone pathway to be of importance Table 3. Studies have shown that the pathophysiology of DKD involves K27-linked polyubiquitination at lysine 80 in the hub gene Pten.[30] Enrichment analysis of the hub genes of the liver DEGs has shown NAFLD pathways along with HIF-1 signaling, AMPK signaling and generalized cancer pathway to be enriched (Table 3). In tune with NAFLD, lipid biosynthesis and metabolism processes have also been enriched in the hub genes from the liver DEGs (Table 3).

In this study, potential drug candidates were also explored in order to put forth therapeutic interventions that targets commonly involved hub genes or hub genes unique to both DKD and NAFLD. Bioinformatics analysis is exceptionally suited in this regard because it accelerates drug target identification, drug candidate screening and refinement.[31] In 333, 305 and 184 drug-gene interactions (DGI) were found after mining the DGIdb database for the three sets of hub genes. After ADMET analysis by SwissADME web tool only 9 candidates were found to be viable as potential drugs (Table 4). These drugs can be divided into two categories- those that target hub genes from Common DEGs (Serial 1-5 in Table 4) and those that target hub genes from kidney and liver DEGs (Serial 6-9

in Table 4). The drugs may thus be repurposed for the intervention of said genes.

Ppar alpha gene (Ppara) is an important hub gene belonging to the Ppar metabolic pathway which has been found to be a predominantly enriched pathway responsible for both DKD and NAFLD as identified by the current study. It is encouraging to note that two potential drug candidates viz. fenofibrate and clofibrate, belonging to the drug class Fibrate, which show agonist behavior towards Ppara, have been identified by this bioinformatics study. This shows the advantage of such bioinformatic exploration in identifying existing drug targets that may be repurposed and developed towards targeting important genes responsible for DKD and NAFLD, besides their current use. Similarly, the drug alpelisib has been identified to have interaction with the hub gene Sgk1 which is part of the FoxO pathway, enriched in DKD and NAFLD. Further study on Alpelisib with reference to Sgk1 may derive the former to be a feasible therapeutic intervention for DKD and/or NAFLD. Drug-gene interaction has been found for bortezomib and ribociclib and the hub gene Notch1, where the latter has been known to regulate proteinuria in DKD, making these drug candidates useful leads to be studied further. Rest of the drug candidates given in Table 3 also represent those drugs interacting with hub genes that are unique to DKD and/or NAFLD which helps to narrow down the field of potential candidates that have finest chance of being developed into therapeutic interventions targeting these two diseases.

This study has elaborated hub genes that are typically involved in the etiology of both DKD and NAFLD as a consequence of diabetes, which can be used as targets for therapeutic intervention as well as points of further study. Enriched pathways and processes provide an insight into the mechanisms that may be prevalent in the development and progression of both diabetic disease conditions. Such mechanisms may be further probed in order to get a comprehensive picture of DKD and NAFLD in diabetic patients. Identification of viable drug candidates provides an impetus into studying and developing lead compounds specific for DKD and NAFLD in diabetes patients which have been lacking till date.

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