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REVIEW ARTICLE

The *HNF1B* mutations and deletion associated with diabetes and their resulting diabetic phenotypes: a systematic review

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Abstract

Objective Mutations or deletion in *HNF1B* gene has been found to be related to a special type of monogenetic diabetes (*HNF1B*-DM). However, the phenotypic features of *HNF1B*-DM and the related gene abnormalities remain unclear.

Methods We systemically reviewed the literature associated with *HNF1B*-DM in PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang databases. The mutations and clinical data of *HNF1B*-DM were recorded. The phenotypes between mutations and deletion in *HNF1B* were analyzed.

Results In total, 261 eligible individuals were included. 64 mutations were reported in 134 patients, and another 127 patients carried a large deletion in *HNF1B* gene. The mutations were distributed throughout from exons 1 to 7, including missense, nonsense, frameshift, and splice site mutation. Body weight index (BMI) was available for 69 patients; 55 patients (79.7%) were normal or underweight. Of the 131 patients with available family history, 105 (80.2%) reported a family history of diabetes. Data on age at diagnosis of diabetes was recorded in 210 patients with a mean of 23.7 years. Estimated glomerular filtration rate was recorded in 52 patients with a median of 47.00 ml/min per 1.73 m^2. Renal cysts were in 78.9%, pancreatic dysplasia in 78.6%, and hypomagnesemia in 64.3% of the patients. The patients with *HNF1B* deletion had different diabetic phenotypes from the patients with *HNF1B* point mutation.

Conclusions *HNF1B*-DM patients were with younger onset age, normal or low BMI, renal cyst, pancreatic dysplasia, and hypomagnesemia. The patients should be recommended for genetic testing to differentiate *HNF1BDM* from other young-onset diabetes earlier.

Keywords *HNF1B* · MODY5 · Renal cyst and diabetes syndrome · Diabetes · Glomerular filtration rate

Background

Maturity-onset diabetes of the young (MODY) defines a dominantly inherited form of diabetes mellitus, characterized by diagnosis in children or young adults. MODY results from heterozygous defects in 14 genes affecting pancreatic islet function. The four most common causes of MODY are mutations in *HNF1A* (MODY3), *GCK* (MODY2), *HNF4A* (MODY1), and *HNF1B* (MODY5) [1].

HNF1B, located at 17q12, consisting of 9 exons, is a transcription factor comprising three domains: an N-terminus dimerization domain, a highly conserved DNA-binding domain, and a C-terminus transactivation domain [2]. It not only plays an important role in the development of various organs such as the kidney, pancreas, liver, and reproductive organs but also regulates the expression of multiple genes related to glucose metabolism. Hence, heterozygous mutations or deletion in *HNF1B* resulted in a multisystem disorder including diabetes, renal structural abnormalities, pancreatic hypoplasia or pancreatic exocrine abnormalities, liver dysfunction, and reproductive system development abnormalities. Renal cysts and diabetes are the most common clinical manifestations of *HNF1B*-associated disease referring to the name of RCAD syndrome [3]. Whole gene deletion of *HNF1B* is part of the 17q12 deletion syndrome. The deletion length of 17q12 deletion syndrome is about 1.4 Mb and contains about 15 genes, of which *HNF1B* gene is one.

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The phenotypes of diabetes caused by mutations and whole gene deletion of *HNF1B* are highly heterogeneous. A previous study revealed that approximately 50% of these cases lacked a family history of diabetes [4]. In addition, the combined organ abnormalities are relatively hidden; it is easily misdiagnosed as type 1 or type 2 diabetes. However, the treatment and prognosis are very different. This review will concentrate on the clinical and genetic features of *HNF1B*-DM to help clinicians know about this type of diabetes.

Materials and methods

Searching strategy and data sources

A comprehensive search on the PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang was performed using the terms 17q12, diabetes mellitus type MODY5, Maturity onset diabetes of the young 5, MODY5, *TCF2*, *TCF-2*, *HNF1B*, *HNF1-B*, *HNF-1B*, *HNF1-beta*, *HNF1beta*, hepatocyte nuclear factor 1B, hepatocyte nuclear factor 1 beta, and renal cysts and diabetes syndrome (RCAD). We imposed a language restriction (English) and applied inclusion criteria for patients with *HNF1B*-DM based on previous studies from 1997 to January 2022. The inclusion criteria were as following: (1) The variants in diabetes patients were regarded as mutations if they were classified as pathogenic or likely pathogenic according to the guidelines of the American College of Medical Genetics and Genomics and Society for Molecular Pathology (ACMG-AMP) guidelines [5]. According to the ACMG-AMP guidelines, we used two or more lines of computational evidence (PROVEAN and SIFT, http://provean.jcvi.org, PolyPhen2, http://genetics.bwh.har-vard.edu/pph2, MutationTaster, http://www.mutationtaster.org; MutationAssessor, http://mutationassesso-r.org) to support for pathogenic gene 3 (PP3) harmful effects. The databases, 1000 Genomes (https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/) and gnomAD (http://gnomad-sg.org/), were used to support for a moderate piece of evidence for pathogenicity (PM2). (2) The literature provided the data of FBG or HbA1c or the use of glucose-lowering therapy. The exclusion criteria were as follows: (1) literature on animal or cell experiments rather than case studies, (2) patients with a MODY5 phenotype without genetic testing results, (3) diabetic patients carrying HNF1B variants but not mutations, (4) patients with *HNF1B* mutations who had abnormalities in kidney or other organs but without diabetic phenotype, and (5) repeat patients or literature. The flow chart (Fig. 1) showed the reasons for determining of eligible studies.

After careful reading of the included literature, the data of every eligible patients on diabetic phenotypes were extracted to analyses from published literature using a self-made form: country or regional origin, sex, age, age at diagnosis, family history of DM, family history of renal abnormalities, body mass index (BMI), treatment of diabetes, fasting blood glucose (FBG), fasting C-peptide (FCP), HbA1c, other serum

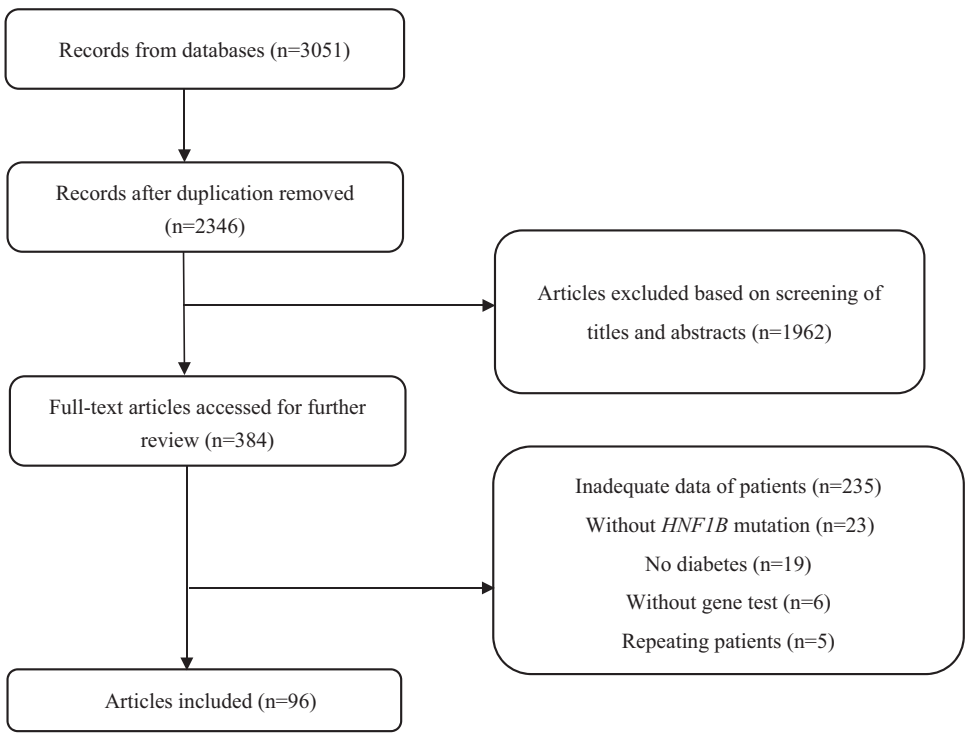

Fig. 1 Literature review inclusion process

indices, the presence of hypomagnesemia, the presence of hyperuricemia, the presence of elevated liver enzymes; renal manifestations, pancreatic manifestations, reproductive manifestations confirmed by ultrasound, CT, or MRI. Abnormal renal manifestations we collected included renal cyst, renal agenesis, renal malformation, single kidney, renal atrophy, renal hyperechogenicity, ectopic kidney, hydronephrosis, hydroureter, and renal transplantation but excluded kidney stone. Abnormal pancreatic manifestations we collected included pancreatic hypoplasia and pancreatic exocrine function. Abnormal reproductive manifestations we collected included vaginal agenesis, absence of uterus or ovaries, bicornate uterus, and epididymal cyst.

Statistical method

Continuous variables with a normal distribution were expressed as mean and standard error (±SD), and continuous variables with a non-normal distribution were expressed as the median and interquartile range (25–75th percentile). Categorical variables are expressed as percentages (%). The *t*-test and the Mann–Whitney *U* test were used to compare the mean or median values between the groups with SPSS 17.0 software. The rates were compared by Fisher's exact test. p values < 0.05 was considered statistically significant.

Results

General data

A total of 96 literature [6–101], including 59 mutations and two types of deletion in 261 diabetes patients, were included in this study. Ethnic or regional data were available for 129 patients, including 74 from the Caucasus, 29 from Japan, 6 from China, 3 from Turkey, 14 from India, 2 from Korea, and 1 from Vietnam.

Gene abnormalities

64 mutations were reported in 134 patients, and another 127 patients carried deletion in *HNF1B*. The type of mutation included missense, nonsense, frameshift, and splice site. The mutations were distributed throughout from exon 1 to 7. The mutation detected in exons 8 and 9 had not been reported (Fig. 2 and Supplementary Table 1). Most of them were located in the DNA-binding domain, and a few were located in the N-terminal dimer domain and the C-terminal transcriptional activation domain. There was no mutation "hot spots"; most of the mutations were private, but Arg295His and IVS2 + 1G > T had been reported in more than one family. 47 patients were recorded whether their mutations were De novo and De novo mutation was reported in 23 patients (48.9%). There were two types of deletion reported, including exon-deletion and whole gene deletion. Only six patients were exon-deletion.

Diabetic phenotype features

The clinical data of the patients is shown in Table 1. Sex data was available for 222 patients, 95 of which were male. Age data was available for 182 patients; the mean age was 32.3 years old, ranging from 1 to 80 years old. Family history of diabetes data was available for 131 patients, and 105 patients (105/131, 80.2%) had a family history of DM. 28 patients were recorded whether they had a family history of

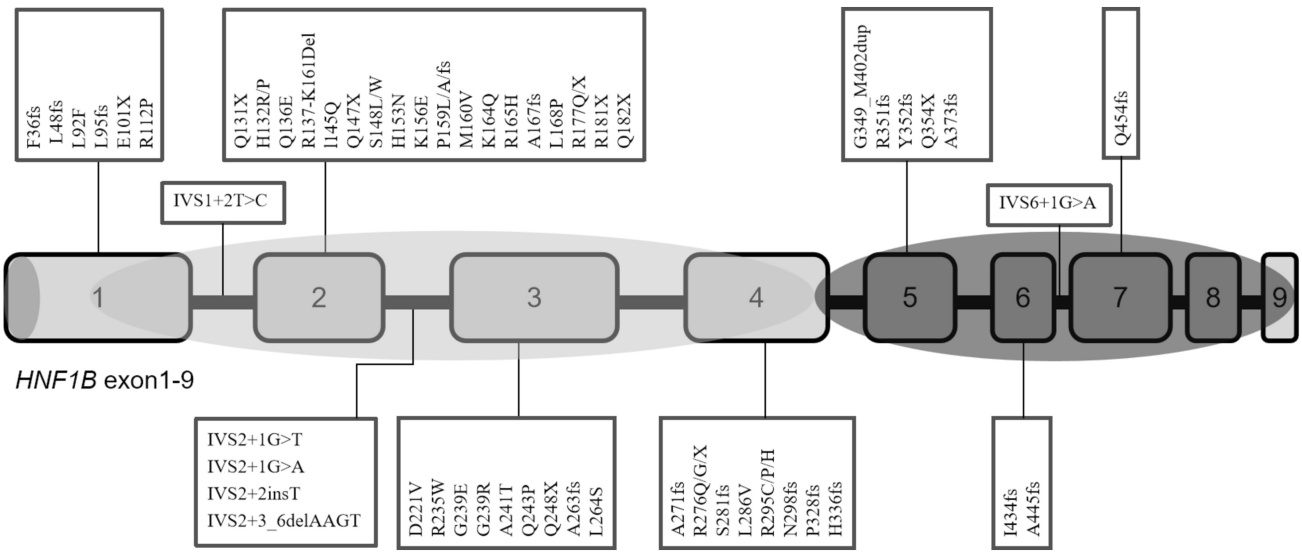

Fig. 2 The mutations in *HNF1B* related to diabetes

Table 1 The clinical features of the patients with *HNF1B*-related diabetes

Subjects	No. of patients	Data
Sex (male)	95/222	42.8%
Age (year)	182	32.31 ± 16.2
Onset (year)	210	23.7 ± 13.0
BMI (kg/m^2)	69	21.8 ± 4.7
Family history	105/131	80.2%
FBG (mmol/L)	48	9.8 (7.1–19.7)
FCP (ng/mL)	41	0.60 (0.10–1.40)
HbA1c (%)	50	7.2 (6.3–10.8)
eGFR (mL/min per 1.73 m^2)	52	47.0 (36.2–66.3)
Creatinine (μmol/L)	52	116.5 (88.6–206.1)
Ketosis	15/37	40.5%
Insulin	129/155	83.2%
Renal imaging abnormalities	186/208	89.54%
Renal cyst	151/206	78.9%
Bilateral renal cysts	37/53	69.8%
Multiple renal cysts	45/56	80.4%
Proteinuria	16/34	47.1%
Elevated liver enzymes	57/113	50.4%
Pancreas dysplasia	55/70	78.6%
Reproductive system abnormalities	19/43	44.2%
Hypertension	14/32	43.8%
Hypomagnesemia	27/42	64.3%
Hypokalemia	5/19	26.3%
Hyperuricemia	26/56	46.4%

Results are expressed as mean ± standard deviation, or as median (IQR)

BMI body mass index, *FBG* fasting blood glucose, *FCP* fasting c-peptide, *HbA1c* glycosylated hemoglobin, *eGFR* estimated glomerular filtration rate

renal abnormalities or not, and 15 of these patients did (15/28, 53.6%). Data on age at diagnosis of diabetes was recorded in 210 patients with a mean of 23.7 years, ranging from 1 to 78 years and 64.4% of the patients were younger than 25 years. BMI was available for 69 patients. The mean BMI was 21.8 kg/m^2. According to WHO standard, 20 patients (20/69, 29.0%) were underweight (< 18.5 kg/m^2), 35 patients (35/69, 50.7%) were normal, 11 patients (11/69, 15.9%) were overweight (> 25.0 kg/m^2), and 3 patients (3/69, 4.3%) were obese (≥ 30.0 kg/m^2).

FBG was recorded in 48 patients with a median of 9.8 mmol/L (normal range 3.9–6.1 mmol/L). A total of 41 patients were recorded with the FCP. The median of FCP was 0.60 (0.10–1.40)ng/mL. HbA1c was recorded in 50 patients with a median of 7.2 (normal range 4–6%). Estimated glomerular filtration rate (eGFR) was recorded in 52 patients with a median of 47.00 mL/min per 1.73m^2. Serum creatinine was recorded in 52 patients with a median of 116.5 mmol/L. The presence or absence of ketosis was recorded for 37 patients, of whom 15 had.

Among the 208 patients mentioning the results of the renal imaging examination, 186 patients were abnormal, including 151 patients with renal cyst and 35 patients with other renal abnormalities. The diameter of renal cysts was recorded in 21 patients, and that in 19 patients was less than 2.5 cm. Among the 70 patients mentioning the results of pancreatic imaging, 55 patients had pancreatic hypoplasia. Among the 19 patients recorded with pancreatic exocrine function, 13 patients had pancreatic exocrine dysfunction. The clinical manifestations of the pancreatic exocrine dysfunction included asymptomatic, abdominal pain, diarrhea, and weight loss. Among the 43 patients mentioning the results of germline data, 19 were abnormal. The level of liver enzymes was recorded in 113 patients, of which 57 were elevated. Serum magnesium levels were recorded in 42 patients, of which 27 had hypomagnesemia. Serum uric acid levels were recorded in 56 patients, of which 26 had hyperuricemia. Hypokalemia were recorded in 5 patients from 19 patients with a report of serum potassium levels.

The treatments at diagnosis were recorded for 155 patients. 129 patients were treated with insulin, 13 patients underwent diet therapy only, 11 patients were given oral hypoglycemic agents without insulin, and 2 patients used liraglutide only. Among the 129 patients receiving insulin, 13 patients combined oral hypoglycemic drugs, and 116 patients received insulin monotherapy.

The phenotypes caused by point mutation and whole gene deletion were different (Table 2). The patients with whole gene deletion had a later onset age of diabetes (25.9 ± 13.6 vs. 22.2 ± 12.3 years old, $p = 0.043$), a lower serum creatinine [104.2 (73.5–123.8)μmol/L vs. 175.0 (112.7–256.9) μmol/L, $p = 0.003$], a lower risk of proteinuria (12.5% vs. 57.7%, $p = 0.043$), a higher risk of hypomagnesemia (79.3% vs. 30.8%, $p = 0.005$), and lower prevalence of hyperuricemia (26.5% vs. 81.0%, $p < 0.001$) than the patients with point mutation.

Conclusion

This is the first systematic review of the *HNF1B* mutations and deletions related to diabetes and their diabetes phenotype to date. We collected data from 96 studies, including 261 participants. All 64 included mutations in patients were confirmed by the ACMG-AMP guideline. The mutations were only distributed in exons 1–7. *HNF1B*-related diabetes phenotype has a particular feature: an early onset age, normal or underweight (79.7%), high incidence of renal cysts (78.9%), and pancreas hypoplasia (78.6%), a different phenotype between point mutations and deletions. Patients with these characteristics should receive genetic testing as

Table 2 Comparison of clinical features between the different genotypes

Subjects	Deletion		Mutations		*p*
	No. of patients	Data	No. of patients	Data	
Age (year)	91	32.0 (18.0–43.0)	91	29.0 (17.5–40.50)	0.489
Onset (year)	88	25.9 ± 13.6	122	22.2 ± 12.3	0.043*
BMI (kg/m^2)	24	20.1 (17.8–23.7)	45	22.0 (19.3–24.7)	0.406
FBG (mmol/L)	16	14.05 (8.80–21.70)	32	8.8 (6.85–18.80)	0.057
FCP (ng/mL)	15	0.5 (0.25–0.93)	26	0.67 (0.10–1.43)	0.583
HbA1c (%)	23	8.5 ± 3.4	27	8.8 ± 3.2	0.715
eGFR (mL/min per 1.73m^2)	33	47.0 (38.0–71.5)	19	47.0 (33.1–60.0)	0.403
Creatinine (μmol/L)	26	104.2 (73.5–123.8)	26	175.0 (112.7–256.9)	0.003**
Sex	104	Male = 41 Female = 63	118	Male = 54 Female = 64	0.346
Family history	55	No = 13 Yes = 42	76	No = 13 Yes = 63	0.382
Ketosis	14	No = 9 Yes = 5	23	No = 13 Yes = 10	0.738
Insulin	62	No = 13 Yes = 49	93	No = 13 Yes = 80	0.278
Renal imaging abnormalities	96	No = 11 Yes = 85	112	No = 11 Yes = 101	0.882
Renal cyst	95	No = 23 Yes = 72	111	No = 32 Yes = 79	0.528
Bilateral renal cysts	27	No = 6 Yes = 21	26	No = 10 Yes = 16	0.241
Multiple renal cysts	30	No = 5 Yes = 25	26	No = 6 Yes = 20	0.738
Proteinuria	8	No = 7 Yes = 1	26	No = 11 Yes = 15	0.043*
Elevated liver enzymes	63	No = 34 Yes = 29	50	No = 22 Yes = 28	0.345
Pancreas imaging abnormalities	36	No = 10 Yes = 26	34	No = 5 Yes = 29	0.247
Reproductive system abnormalities	20	No = 14 Yes = 6	23	No = 10 Yes = 13	0.125
Hypertension	9	No = 3 Yes = 6	23	No = 15 Yes = 8	0.132
Hypomagnesemia	29	No = 6 Yes = 23	13	No = 9 Yes = 4	0.005**
Hypokalemia	11	No = 8 Yes = 3	8	No = 6 Yes = 2	1.000
Hyperuricemia	35	No = 26 Yes = 9	21	No = 4 Yes = 17	< 0.001**

Results are expressed as mean ± standard deviation, or as median (IQR)

BMI body mass index, *FBG* fasting blood glucose, *FCP* fasting C-peptide, *HbA1c* glycosylated hemoglobin, *eGFR* estimated glomerular filtration rate

* $p < 0.05$; ** $p < 0.01$

early as possible to avoid misdiagnosis as type 1 or type 2 diabetes.

The reported point mutations were only distributed in exons 1–7 and mainly in the DNA-binding domain, indicating that mutations in this domain may have a strong role in the development of diabetes. A previous study used fast and accurate computational approach to understanding the genotype–phenotype relationships in HNF1B [102]. Our results also show a high rate of de novo mutations (48.9%) in patients with *HNF1B*-DM, which was consistent with the results of two large cohort studies that 50 ~ 60% of diabetes cases carried de novo mutations or deletions in *HNF1B* [4,

71]. Partial or whole gene deletion was recorded in nearly half of patients (127/261, 48.7%). A previous study showed it was a frequent cause of *HNF1B*-DM in a large Caucasian cohort [17]. It was also related to impaired fasting glucose [17] and impaired glucose tolerance [14, 42]. Large genomic rearrangements of TCF2 were easy to be missed by conventional gene screening methods.

HNF1B-DM patients had an early onset, and most of them were adolescents and young adults with diabetes. This was inconsistent with the results of a previous multicenter retrospective cohort study, revealing that the onset age of diabetes was > 25 years in 57% of 159 *HNF1B*-DM patients [103]. While another multicenter cohort study showed that the mean age of diagnosis of *HNF1B*-DM was 26 years old [104]. A meta-analysis of 211 *HNF1B* gene deficiency patients from 47 articles found that 95 patients (45%) had diabetes. The mean age at diagnosis of diabetes was 23.7 years [3]. The differences in age at diagnosis of diabetes across studies may be due to different inclusion criteria in terms of patient age, race or region. Therefore, MODY5 often occurred in adolescence rather than in the neonatal period. However, Several patients with *HNF1B* gene abnormality were reported to have transient or permanent neonatal diabetes [80, 82]. These results suggested that the dysfunction of islet β cells was present in early life in *HNF1B*-DM patients and worsens under stress, leading to diabetes. Furthermore, a large European cohort study [103] revealed that insulin secretion in patients with *HNF1B*-DM did not decrease with the increase of the course of disease, while a short series from Japan suggested patients had severe insulin secretion defects [48]. Meanwhile, most of the patients in our review with *HNF1B*-DM were not obese. Therefore we hypothesized that the severe defection of insulin secretion was the primary cause of *HNF1B*-DM.

Renal imaging abnormalities, particularly renal cysts, were found in most of our patients, similar to the previous cohort studies [19, 103]. Renal cysts can be unilateral or bilateral and 69.8% were bilateral. This should alert the physician that renal ultrasonography may orientate an etiological diagnosis of no autoimmune diabetes. A study, that included fifty unrelated young diabetic patients combined with renal abnormalities from India, revealed that 10% of subjects harbor HNF1B mutations [99]. It suggested that clinicians should consider the possibility of MODY5 in diabetic patients with nephropathy, particularly renal cysts. Although we did not review the renal function of the patients, a decreased renal function was also reported in a large cohort of patients with *HNF1B*-DM [103]. The high presence of hypomagnesemia in patients with *HNF1B*-DM may related to the decreased renal function and renal magnesium wasting. Because *HNF1B* is associated with transactivating of the *FXYD2* gene, which encodes the γ subunit of Na^+-K^+-ATPase and is involved in Mg^{2+} transport in the renal tubules [65, 105].

Our study also found that there are significant differences between *HNF1B* point mutation patients and *HNF1B* deletion patients. The patients with *HNF1B* deletion had a later onset age of diabetes than the patients with point mutation. The result was inconsistent with a previous cohort study involving 159 adult *HNF1B*-DM patients that found no significant difference in the age of onset of diabetes between the two groups [103]. It may be caused by the different sample size and age of the study population in the two studies, or it may be related to the other 14 genes missing in the 17q12 deletion syndrome. The patients with *HNF1B* deletion had a lower serum creatinine, a lower risk of proteinuria, a lower risk of hypomagnesemia, and lower prevalence of hyperuricemia than the patients with point mutation. A large adult cohort study analysis containing 156 *HNF1B*-DM patients suggested that compared with point mutation patients, *HNF1B* deletion patients had a relatively good renal prognosis [103]. The results revealed that the patients with *HNF1B* deletion may had better renal function. In a previous cohort of children with *HNF1B*-associated nephropathy, serum uric acid elevated faster in patients with point mutations than in those with whole-gene deletions. This suggests that *HNF1B* point mutation is more damaging to the kidney than the whole gene deletion. It is speculated that the mutated protein may cause endoplasmic reticulum stress, leading to renal tubular cell damage, and further causing renal interstitial fibrosis, thereby affecting renal function. The whole gene deletion does not lead to the accumulation of abnormal proteins in the endoplasmic reticulum absent of stress and renal injury. It is worth noting that hypomagnesemia may be an obvious feature in the early stage of the disease. When renal function decreased significantly, hypomagnesemia is often masked, and blood uric acid is also significantly increased at this time.

Our study has several limitations. First, the data of included patients were incomplete, especially the data on blood lipids, which was helpful in exploring the relationship between *HNF1B*-DM patients and insulin resistance. Second, The data on blood glucose and glycosylated hemoglobin were not recorded whether they were before or after treatment. Third, some patients in several larger cohort studies were excluded because raw data could not be collected for each patient.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-024-01319-3.

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Author contribution Professor Han Xueyao designed the review, and Yating Li completed the literature screening, data collection and analysis, and the writing of the article. The review was not registered.

Data availability All datasets are available from the corresponding authors upon reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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