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REVIEW ARTICLE

The emerging role of CAMK1D in diabetes, metabolism and feeding behaviours: A mechanistic systematic review

Livio Tarchi[1] | **Annalisa Di Giacomo**[2] | **Lorenzo Bonacchi**[1] | **Andrea Di Santo**[3] | **Paolo Rovero**[3] | **Chiara Sassoli**[4] | **Rachele Garella**[4] | **Roberta Squecco**[4] | **Gianluca Villa**[1] | **Romina Nassini**[1] | **Francesco De Logu**[1] | **Tiziana Pisano**[2] | **Valdo Ricca**[1] | **Giovanni Castellini**[1]

[1]Dipartimento di Scienze della Salute, Universita degli Studi di Firenze, Florence, Italy

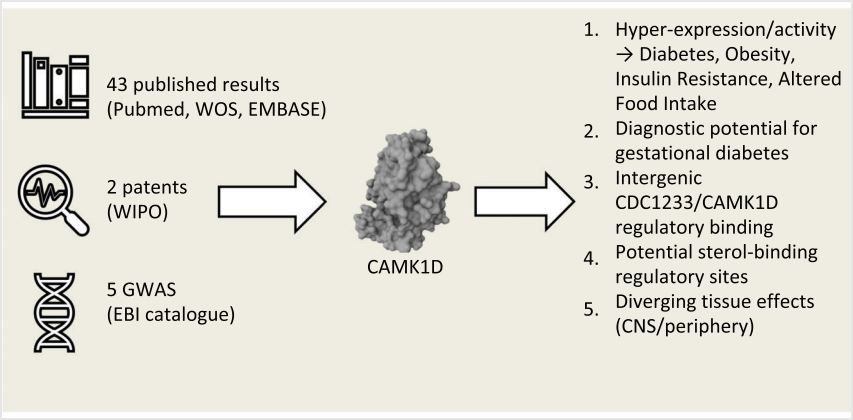
[2]Dipartimento delle neuroscienze e genetica medica, Azienda Ospedaliero Universitaria Meyer, Florence, Italy

[3]Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino, Universita degli Studi di Firenze, Florence, Italy

[4]Dipartimento di Medicina Sperimentale e Clinica, Universita degli Studi di Firenze, Florence, Italy

Correspondence
Livio Tarchi, Dipartimento di Scienze della Salute, Universita degli Studi di Firenze, Florence, Italy.
Email: livio.tarchi@unifi.it

Graphical Abstract



This systematic review synthesizes evidence from published studies, GWAS and grey literature (patents) to show that CAMK1D is implicated in diabetes, obesity, insulin resistance and altered feeding behaviours, with diagnostic potential and mechanistic relevance through regulatory binding and tissue-specific effects.

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[3]Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino, Universita degli Studi di Firenze, Florence, Italy

[4]Dipartimento di Medicina Sperimentale e Clinica, Universita degli Studi di Firenze, Florence, Italy

Correspondence
Livio Tarchi, Dipartimento di Scienze della Salute, Universita degli Studi di Firenze, Florence, Italy.
Email: livio.tarchi@unifi.it

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Abstract

Background: Diabetes, metabolic disorders and feeding behaviours continue to pose significant public health challenges. Calcium/calmodulin-dependent protein kinase ID (CAMK1D) has recently emerged as a pivotal molecule potentially bridging peripheral metabolic control with central appetite regulation. Therefore, a comprehensive review was performed to critically evaluate and synthesize current evidence regarding the role of CAMK1D in diabetes, metabolic processes and feeding behaviours.

Main text: The review assessed both published results (263 non-duplicate studies; across Pubmed, WebOfScience and EMBASE) and the grey literature (including 14 patents, 3 clinical trials). Results from 43 unique studies, 2 patents and 5 genome-wide association studies were finally summarized. CAMK1D modulates both metabolic processes and feeding behaviours, exhibiting tissue-specific dynamics and diverging regulatory control either in the central nervous system (i.e., hypothalamic nuclei regulating appetite and satiety) or in the periphery (i.e., pancreatic beta cells). Genetic studies highlighted significant associations between CAMK1D polymorphisms and increased susceptibility to diabetes, obesity and altered feeding behaviours.

Conclusions: CAMK1D represents an emerging molecular target with promising implications for the treatment of a wide range of clinical conditions. However, further large-scale, mechanistic and longitudinal studies are warranted to validate its role across physiological and pathophysiological conditions, as well as to explore its future therapeutic potential.

KEYWORDS
anorexia nervosa, bulimia nervosa, calcium/calmodulin dependent protein kinase ID, CaM-K1, CKLiK

1 | INTRODUCTION

Diabetes mellitus, metabolic dysregulation and altered feeding behaviours represent significant global health challenges,[1–3] which are potentially associated with one other through complex physiological pathways.[3–6] Recent advances in molecular biology have underscored the importance of signal transduction proteins in regulating metabolic homeostasis and energy balance.[7–10] Among these, calcium/calmodulin-dependent protein kinase ID (CAMK1D) has emerged as a protein of interest given its putative roles in modulating insulin signalling, glucose metabolism and neural regulation of appetite,[11] being mostly expressed in the central nervous system within mammals.[12] The convergence of evidence from genetic, biochemical and functional studies suggests that CAMK1D may serve as a critical nexus in the interplay between metabolic control and feeding behaviours.

Despite the increased interest in the scientific literature on multifaceted functions of CAMK1D in diabetes, metabolic regulation and in the control of feeding behaviours, its precise contribution to the pathophysiology of diabetes and related metabolic disorders remains incompletely understood. Consolidated evidence by genome-wide association studies (GWAS) has implicated CAMK1D in pathways that influence insulin secretion and sensitivity,[13,14] which are fundamental to maintaining glucose homeostasis.[15,16] Concurrently, research exploring the neural substrates of feeding behaviour suggests that CAMK1D may be involved in central mechanisms that regulate appetite and energy expenditure.[11] This wide range of functions underscores a compelling need for a systematic synthesis of the available evidence on the role of CAMK1D in both physiological and pathophysiological conditions.

Therefore, this systematic review aims to widely examine the emerging role of CAMK1D in diabetes, metabolism and feeding behaviours. By comprehensively assessing evidence from published research, unpublished clinical trials patents and from genetic studies, we seek to clarify the extent to which CAMK1D can be considered a viable target for future therapeutic interventions. Moreover, this review will address existing gaps in the literature and propose directions for future research.

2 | MATERIALS AND METHODS

The present systematic review has been redacted in accordance with PRISMA 2020 guidelines.[17] Inclusion and exclusion criteria were specified according to Sample, Phenomenon of Interest, Design, Evaluation and Research Type (SPIDER, Table 1).[18] This review's protocol was pre-registered and is available at the stable link: https://osf.io/jbsmd.

TABLE 1 SPIDER criteria.

Parameter	Criteria
Sample	Humans, animals, in vitro
Phenomenon of Interest	CAMK1D (polymorphisms, physiological role, role in clinical conditions)
Design	Any study design
Evaluation	Feeding behaviours, food intake, eating disorders, diabetes and metabolism
Research type	Original contributions, not reviews

Abbreviations: CAMK1D, calcium/calmodulin-dependent protein kinase ID; SPIDER, sample, phenomenon of interest, design, evaluation and research type.

2.1 | Information sources and search strategy

The authors used the electronic databases PubMed, WebOfScience and EMBASE in order to retrieve studies. The following string was used for the systematic search: '(CAMK1D) OR (CKLiK) OR (CaM-K1) OR (CaMKID) OR (calcium calmodulin dependent protein kinase ID) OR (calcium calmodulin dependent protein kinase 1D)'. The terms included in the string were chosen to reach a broader scope over the published scientific literature. PRISMA2020 was used in order to graphically represent the flow of information from the search to the final inclusion.[19] Results in the grey literature were also retrieved, searching each term (i.e., each synonym of CAMK1D) in the search string, individually, in 'clinicaltrials.gov' (https://clinicaltrials.gov). Patents were also retrieved, searching for the term 'CAMK1D' through 'patentscope', as hosted by the World Intellectual Property Organization (WIPO, https://patentscope.wipo.int). Clinical phenotypes and associated traits were retrieved in the European Bioinformatics Institute (EBI) GWAS Catalogue (https://www.ebi.ac.uk/gwas).

The last search for published literature, unpublished results, patents, clinical phenotypes and associated traits was run in March 2025. A single, standardized and quantitative appraisal for risk of bias was possible for the current systematic review, given the heterogeneity in study designs and involved procedures for included studies (humans, animals, tissue studies, in vitro) and the lack of validated instruments adapted for assessing this wide range of studies. Rather, according to PRISMA 2020 guidelines,[17] risk of bias was summarized by presenting conflicting evidence and highlighting potential sources of heterogeneity among study results.

2.2 | Data selection process

L.T. and A.D.G. independently assessed the abstracts of potentially eligible studies. Eligibility assessment was performed in an unblinded standardized manner. If there were doubts concerning the eligibility of the study for inclusion, the reviewers examined the full text of the articles. The published protocol required consensus in case the authors disagreed on the inclusion of a specific study. In case the opinion was not unanimous, a majority vote would have been taken between all authors. The authors agreed on all the eligibility assessments of the studies, and no consensus vote needed to take place. L.T. and A.D.G. independently extracted several categories of data from each included study, namely, sample (humans, animals, in vitro), design (observational or interventional; cross-sectional or longitudinal) and construct under evaluation (diabetes, obesity and metabolism and or food intake regulation/feeding behaviours/eating disorders).

3 | RESULTS

Of the 263 other screened studies (from the published scientific literature), 43 were finally included. A flowchart of included studies is graphically illustrated (Figure 1). Of these 43 published studies, 24 pertained to CAMK1D's role in diabetes (55.81%), 14 CAMK1D's role in obesity or metabolic traits (32.56%) and 5 CAMK1D's role in food intake control (11.63%).

Fourteen patents were retrieved. Two were included (MX2012005762; EP3390664) and 12 excluded. Of the 12 excluded patents, seven were duplicates across different countries (duplicates of EP4150334: WO2021229105, CA3178915, US20230228760, AU2021270794 and EP3910331; duplicate of EP3390664: US20200283850 and WO2017103106), three pertained to cancer research (CN116497116, CN119020494 and EP3390664), one (BREP2011069986) pertained to compounds and methods to treat pain and one (JP2019088309) pertained to markers of oocyte competence.

For what concerns unpublished data, three clinical trials were retrieved (NCT04643925, NCT01528800 and NCT01690988). However, none pertained to the role of CAMK1D in diabetes, obesity, metabolic traits, food intake, feeding behaviours or eating disorders.

From the EBI GWAS catalogue, 88 studies (encompassing 112 associations and 65 traits) were manually inspected according to SPIDER criteria (see Methods). Five were finally included.[6,14,20–22]

3.1 | Diabetes

CAMK1D's role in diabetes was evaluated in several genetic and epigenetic studies. Following early GWAS studies describing genetic variants for Type 2 diabetes mellitus,[23,24] subsequent studies attempted to generalize this finding across different world regions, different ethnic populations and wider health burdens associated with diabetes.[13–15,22,25–32]

Studies showed a potential lack of contribution of CAMK1D's polymorphisms in specific ethnic populations,[33,34] highlighting potential geographic and sociocultural factors as underlying the link between CAMK1D and Type 2 diabetes mellitus (Figure 2). Nonetheless, it is unclear whether this lack of significance may have arisen due to issues of reaching sufficient statistical power, as smaller sample sizes were reached in studies reporting null findings.[33–36] Moreover, lack of significance may have also arisen due to lack of inclusion of other single nucleotide polymorphisms (SNPs) beyond those described by previous GWAS studies (especially rs12779790, Table 2). Indeed, multi-ethnic cohorts using a GWAS approach, rather than studying single SNPs, were mostly concordant in identifying an association with the susceptibility to Type 2 diabetes mellitus (Table 2).

In parallel, potential explanations for the link between CAMK1D and diabetes were described by genetic studies linking genetic variants to Type 2 diabetes mellitus in lean individuals,[37] or in individuals without metabolic syndrome.[38] This line of research suggests that the contribution to the risk of diabetes is, at least partly, direct and may survive even when accounting for the potential concurrent contribution of CAMK1D on known risk factors (e.g., obesity, prediabetes and metabolic syndrome).[37–39] To be noted, the most common polymorphisms described in relation to Type 2 diabetes mellitus resulted in an increased recognition of transcription factors and thus increased protein expression (Figure 2).[40]

In parallel, epigenetic studies showed that CAMK1D's hypomethylation may be associated with Type 2 diabetes,[41,42] further suggesting that increased CAMK1D signalling/expression may raise the risk for Type 2 diabetes mellitus. Notably, variants in the intergenic region between CDC123 and CAMK1D have been linked to gestational diabetes.[43] Moreover, preliminary evidence showed that altered protein binding in the same region (CDC123/CAMK1D) may underlie at least one molecular mechanism linking CAMK1D polymorphisms to Type 2 diabetes mellitus (Figure 2).[25,44] In fact, one study described this intergenic region as under the control of

CLINICAL AND TRANSLATIONAL DISCOVERY

TABLE 2 Calcium/calmodulin-dependent protein kinase ID (CAMK1D) and diabetes.

Author (year)	Study type	Disease	Sample size (human studies, ethnicity when available)	Main outcome
Published studies				
Du et al. (2021)[26]	Gene polymorphism, in vivo, human participants	T2DM	2.304 clinical patients: 1.152 T2DM, 1.152 essential hypertension and 1.152 health controls. Northern Chinese Han population	CAMK1D significantly associated with susceptibility to T2DM and essential hypertension (SNP: rs17151584)
Gujarati et al. (2024)[29]	In vivo, animal models (mice)	Diabetic kidney disease		CAMK1D is expressed in the renal proximal tubule and attenuates mitochondrial fission/dysfunction under diabetic conditions
Fogarty et al. (2014)[44]	In vitro, cell assays	T2DM	NA	A GWAS locus for T2DM (CDC123/CAMK1D, SNP: rs11257655) affects transcriptional activity through altered binding of a protein complex, which includes FOXA1/FOXA2. The risk allele increases the expression of CAMK1D through allelic-specific binding of FOXA1 and FOXA2
Xue et al. (2018)[54]	GWAS, in vivo, human participants	T2DM	62 892 T2D cases and 596 424 controls. Mostly European sample	CDC123/CAMK1D (SNP: rs11257655) associated with regulatory mechanisms. Risk allele (same as Fogarty et al.[44]) associated with decreased methylation in the promoter region of CAMK1D, upregulating transcription
Tarnowski et al. (2017)[43]	Gene polymorphism, in vivo, human participants	Gestational diabetes	411 pregnant women. Polish sample	CDC123/CAMK1D (SNP: rs12779790) **NOT** significantly associated with gestational diabetes
Cheng et al. (2014)[41]	Methylation study, in vivo, human participants	T2DM	48 patients with T2DM and 48 age- and gender-matched healthy controls. Chinese Han population	The promoter region of CAMK1D was hypomethylated in the peripheral blood of all subjects. DNA methylation status did not appear to contribute to the risk of T2D
Hu et al. (2023)[53]	Methylation analysis, in vivo, human participants	T2DM, with/without cardiovascular comorbidities	154 individuals: 60 T2DM patients without cardiovascular comorbidities, 51 T2DM patients with cardiovascular comorbidities, 43 healthy controls.Chinese population	CAMK1D **NOT** differently hypomethylated between groups
Lara-Riegos et al. (2015)[33]	Gene polymorphism, in vivo, human participants	T2DM	575 unrelated individuals: 115 T2DM patients and 460 healthy controls. Maya population	CDC123/CAMK1D (SNP: rs12779790) **NOT** significantly associated with T2DM but associated with higher cholesterol and LDL

(Continues)

TABLE 2 (Continued)

Author (year)	Study type	Disease	Sample size (human studies, ethnicity when available)	Main outcome
Imamura et al. (2011)[30]	Gene polymorphism, in vivo, human participants	T2DM	11 530 individuals: 8552 T2DM patients and 2978 healthy controls. Japanese sample	CDC123/CAMK1D (SNP: rs10906115) significantly associated with T2DM, also when controlling for age, sex and body mass index. No significant associations with any metabolic trait, including body mass index, fasting plasma glucose, HOMA-B and HOMA-IR
Grarup et al. (2008)[13]	Gene polymorphism, in vivo, human participants	Glucose tolerance	4516 middle-aged glucose tolerant individuals. Danish sample	CDC123/CAMK1D (SNP: rs12779790) showed significant associations with insulinogenic index, insulin response and the area under the serum-insulin and plasma–glucose curves during an oral glucose tolerance test. The risk allele was thus associated with measures of insulin release, suggesting a role in pancreatic beta-cell function
Schleinitz et al. (2010)[34]	Gene polymorphism, in vivo, human participants	T2DM	2756 individuals: 1443 T2DM patients and 1613 healthy controls. Sorbs and mixed German population	CDC123/CAMK1D (SNP: rs12779790) **NOT** significantly associated with T2DM or metabolic traits
Chen et al. (2013)[61]	Gene polymorphism, in vivo, human participants	T2DM, impaired glucose regulation	3329 individuals: 443 T2DM patients, 1767 impaired glucose regulation and 1119 healthy controls. Chinese She population	CDC123/CAMK1D (SNP: rs12779790) significantly associated with T2DM and metabolic traits
Fromont et al. (2020)[40]	Drug development, in vitro + in vivo, animal model (mice)	Diet-induced obesity	NA	Description of a lead compound that improves insulin sensitivity and glucose control in diet-induced obesity mice, through CAMK1D inhibition
Gamboa-Meléndez et al. (2012)[27]	Gene polymorphism, in vivo, human participants	T2DM	2017 individuals: 1027 T2DM patients and 990 healthy controls. Mexican Mestizo population	CDC123/CAMK1D (SNP: rs12779790) significantly associated with T2DM
Zeggini et al. (2008)[24]	GWAS, in vivo, human participants	T2DM	10 128 individuals. Mostly European population	CDC123-CAMK1D (SNP: rs12779790) significantly associated with T2DM. Note: original GWAS, upon which most subsequent gene polymorphisms studies were based
Omori et al. (2009)[35]	Gene polymorphism, in vivo, human participants	T2DM	Meta-analysis of three sets, total sample 6194 individuals: 3338 T2DM patients and 2856 healthy controls. Japanese sample	CDC123/CAMK1D (SNP: rs12779790) **NOT** significantly associated with T2DM, but borderline significant ($p = .073$)

(Continues)

TABLE 2 (Continued)

Author (year)	Study type	Disease	Sample size (human studies, ethnicity when available)	Main outcome
Sanghera et al. (2009)[57]	Gene polymorphism, in vivo, human participants	T2DM	1317 individuals: 680 T2DM patients and 637 normoglycemic controls. Indian Sikhs sample	CDC123/CAMK1D (rs12779790) associated with T2DM. **NOT** surviving multiple testing correction. However, same SNP significantly associated with fasting insulin levels and HOMA-B
Kang et al. (2009)[31]	Gene polymorphism, in vivo, human participants	Post transplantation diabetes mellitus	589 patients who received kidney transplant, without diabetes. Korean sample	CDC123/CAMK1D (SNP: rs12779790) **NOT** significantly associated with post transplantation diabetes mellitus
Zhou et al. (2010)[36]	Gene polymorphism, in vivo, human participants	T2DM	Meta-analysis of three sets, total sample 3953 individuals: 1912 T2DM patients and 2041 healthy controls. Chinese Han sample	CDC123/CAMK1D (SNP: rs12779790) **NOT** significantly associated with T2DM
Kong et al. (2016)[37]	Gene polymorphism, in vivo, human participants	T2DM	10 001 individuals: 5338 T2DM patients and 4663 healthy controls. T2DM patients were also compared, dividing lean (1125 individuals) and obese patients (1399 individuals). Chinese Han sample	CDC123/CAMK1D (SNP: rs12779790) significantly associated with T2DM in lean individuals
Kong et al. (2020)[55]	Gene polymorphism, in vivo, human participants	T2DM	2734 newly diagnosed T2DM patients and 4041 normal glycaemic controls. Chinese Han sample	CDC123/CAMK1D (SNP: rs12779790) significantly associated with early onset T2DM
Kong et al. (2015)[38]	Gene polymorphism, in vivo, human participants	T2DM, with/without metabolic syndrome	9729 individuals: 5169 T2DM patients and 4560 healthy controls. T2DM patients further divided between those with and without metabolic syndrome: 3651 and 1518, respectively. Chinese Han sample	CDC123/CAMK1D (SNP: rs12779790) significantly associated T2DM in individuals without metabolic syndrome

(Continues)

TABLE 2 (Continued)

Author (year)	Study type	Disease	Sample size (human studies, ethnicity when available)	Main outcome
Cheng et al. (2017)[25]	Computational study, in silico	T2DM	NA	CDC123/CAMK1D may form a protein–protein interaction network with other genes (TCF7L2, MTNR1B, SLC30A8, CDKAL1, IGF2BP2, CDC123, FTO, HHEX, KCNJ11, HNF1B, THADA, JAZF1, WFS1, ADAMTS9, KCNQ1, TSPAN8 and NOTCH2), being characterized as a 'hub' gene
Sun et al. (2016)[32]	Whole genome sequencing, in vivo, human participants	T2DM	200 individuals: 100 with T2DM and 100 healthy controls. Chinese population	CAMK1D single nucleotide variant (synonymous, SNP: rs1757051) associated with T2DM
Author (year)	**Study design**	**Disease**	**Sample size (human studies, ethnicity when available)**	**CAMK1D SNPs (along with statistical significance)**
EBI GWAS catalogue				
Suzuki et al. (2023)[49]	GWAS, in vivo, human participants	T2DM	36 614 T2DM patients and 155 150 controls of Japanese ancestry	rs2997064 ($p = 2 \times 10^{-8}$), rs2815657 ($p = 5 \times 10^{-10}$)
Suzuki et al. (2019)[22]	GWAS, in vivo, human participants	T2DM	2 535 601 individuals (39.7% not of European ancestry), including 428 452 cases of T2D	rs2997064 ($p = 2 \times 10^{-8}$), rs2815657 ($p = 5 \times 10^{-10}$)

Note: In bold, non-significant results for CAMK1D associations with T2DM.

Abbreviations: EBI, European Bioinformatics Institute; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; T2DM, Type 2 diabetes mellitus.

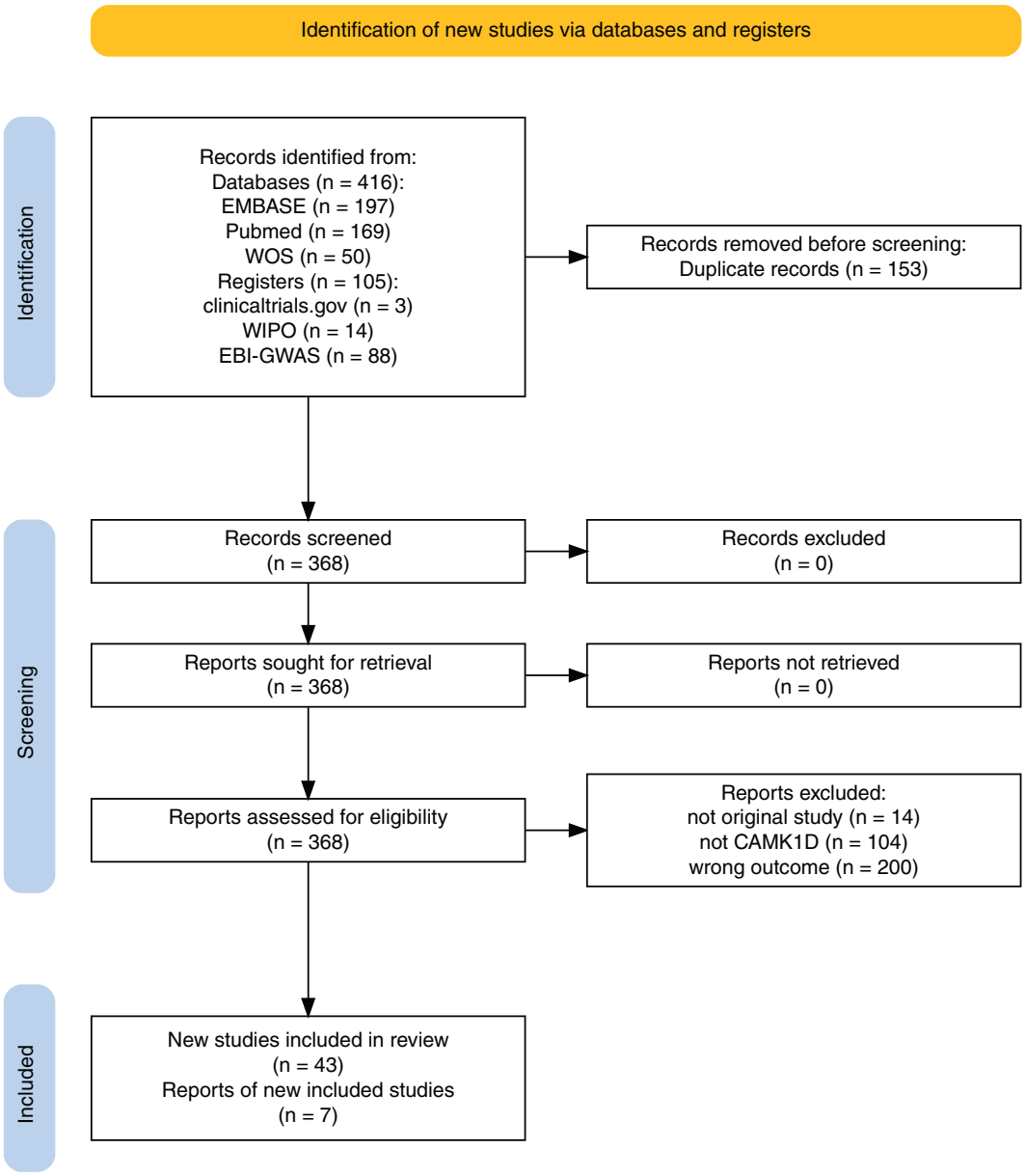

FIGURE 1 Flowchart of included studies.

sterol-regulatory element binding proteins (i.e., upregulating CAMK1D expression; Figure 2).[45] This control by sterol-regulatory elements has significant implications for gender medicine, warranting future studies on the role of calcium signalling in general, and CAMK1D in particular, as contributing to the clinical progression of cardiovascular and metabolic conditions in women.[45]

Importantly, most evidence gathered for the association between CAMK1D polymorphisms and increased susceptibility to Type 2 diabetes mellitus was collected in humans (Table 2). Moreover, most studies were designed after the first identification of the association by an early GWAS study, which was not targeted to CAMK1D alone, reducing the risk of specific biases related to the selective reporting of significant results (i.e., publication bias). Possibly due to the strong degree of evidence for the association, industry interest has risen to develop commercial applications targeting CAMK1D.

More specifically, several patents have been published across different countries by a single entity (Patia Biopharma) to leverage genetic polymorphisms (including CAMK1D) to predict and assess the risk of gestational diabetes (European Patent Office, Publication Number: 3390664, Publication Date: 24.10.2018). A separate patent by a second entity was also retrieved (Center for Research and Advanced Studies of the National Polytechnic Institute), which described specialized methods for the diagnosis of Type 2 diabetes mellitus based on the expression of

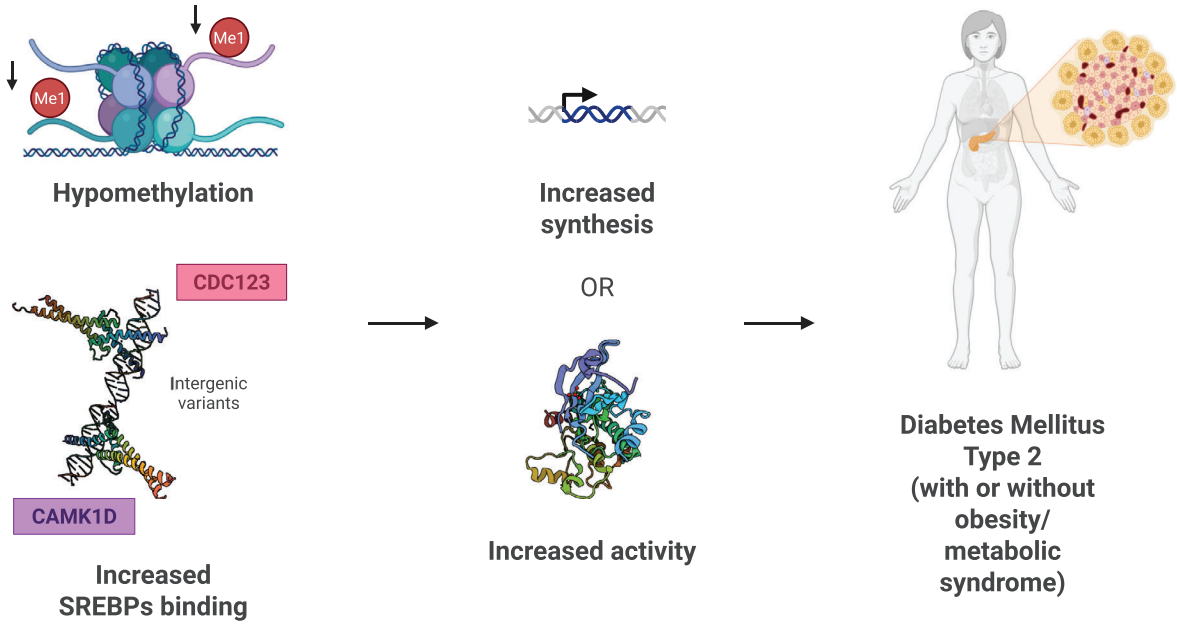

FIGURE 2 Graphical summary of results related to Type 2 diabetes mellitus. Concurrent evidence shows calcium/calmodulin-dependent protein kinase ID (CAMK1D) as positively associated with Type 2 diabetes mellitus, either by increased synthesis (hypomethylation, binding to promoter sites) or increased activity.

different genes, including CAMK1D, as evaluated in white cells retrieved by peripheral blood withdrawal (Publication Number: 2012005762, Publication Date: 21.11.2013).

3.2 | Obesity and metabolism

As previously mentioned, an open question in the field has gathered further attention by later publications, namely, whether CAMK1D's contribution to the risk of developing Type 2 diabetes mellitus may be considered at least partially due to the concurrent increase in other known risk factors. In fact, CAMK1D's polymorphisms have also been associated with the risk of developing obesity (both in adults and children/adolescents),[13,20,21] impaired glucose regulation,[15] insulin secretion[46] or sensitivity,[13,47] altered hepatic glucose regulation,[16] as well as altered respiratory quotient, fat mass deposition and energy storage (Figure 3; Table 3).[21]

Similar results were observed in later GWAS studies, linking CAMK1D to body mass index (BMI) adjusted waist circumference,[20] or upregulated CAMK1D in non-alcoholic fatty liver disease,[10,48] supporting the hypothesis of an indirect contribution to the risk of developing Type 2 diabetes mellitus, possibly through metabolic dysregulation (Figure 3). In fact, genetic polymorphisms in CAMK1D have been associated with diverging levels of total serum levels of total cholesterol and low-density lipoproteins,[33] as well as decreased insulin sensitivity (Figure 3; Table 3).[49]

However, one study showed that CAMK1D polymorphisms were not associated with BMI in children or young adolescents,[50] and a second study showed that CAMK1D associations with insulin resistance are not carried by offsprings of patients with Type 2 diabetes,[51] thus suggesting further caution in drawing causal conclusions on the role of CAMK1D in obesity-associated traits. Importantly, and similarly to the association between CAMK1D and diabetes, most evidence gathered for obesity and metabolic traits was gathered in humans (Table 3). Nonetheless, animal models were more frequently leveraged for this topic.

In particular, animal studies showed that maternal obesity re-programs adipose tissue inflammation in otherwise young lean offspring through CAMK1D upregulation (Figure 3).[52] In summary, these results suggest that CAMK1D may, on one hand, increase the risk of obesity (in one generation) and, on the other, independently, increase the risk of Type 2 diabetes (in offspring) through dysregulated inflammation in adipose tissue,[52] possibly shedding light on the either shared or diverging role of CAMK1D in obesity or diabetes. To be noted, in humans, CAMK1D's polymorphisms have also been observed as underlying diverging interactions with DNA methylation,[53,54] suggesting a role in a wider network of epigenetic control, further granting alternative explanations for the heterogeneous contributions of CAMK1D to either obesity or Type 2 diabetes mellitus.

Similarly to the case of Type 2 diabetes mellitus (Table 2), genetic and physiology studies showed tissue-specificities

TABLE 3 Calcium/calmodulin-dependent protein kinase ID (CAMK1D), obesity and metabolism.

Author (year)	Study type	Disease/Phenotype	Sample size (human studies, ethnicity when available)	Main outcome
Published studies				
Simonis-Bik et al (2010)[58]	2-h hyperglycaemic clamp test, in vivo, human participants	Glucose tolerance	336 participants, 180 normal glucose tolerant and 156 impaired glucose tolerant	Gene variants in CDC123/CAMK1D affected insulin response
Haney et al (2013)[16]	Human hepatocytes, in vitro, cell assay	Hepatic glucose regulation/glycolysis	NA	Through RNAi screening, CAMK1D identified as regulating hepatic gluconeogenesis and glycolysis
Staiger et al (2008)[39]	Gene polymorphism, in vivo, human participants + hyperinsulinemic-euglycemic clamp, in vivo, human participants	Impaired fasting glycaemia, glucose tolerance	1578 individuals: 1139 with normal glucose tolerance, 164 with impaired fasting glycaemia, 152 with impaired glucose tolerance and 123 with impaired fasting glycaemia and impaired glucose tolerance. A subgroup of 513 subjects agreed to undergo a hyperinsulinemic-euglycemic clamp. German sample	CDC123/CAMK1D (SNP: rs12779790) significantly associated with C-peptide at 30 min after oral glucose tolerance test, as well as the area under the curve for C-pep/glucose. However, results did **NOT** survive correction for multiple comparisons
Chunduri et al (2020)[47]	Computational study, in silico	Insulin resistance	NA	CAMK1D was the only gene common among Parkinson's disease, narcolepsy and insulin resistance
Chen et al (2023)[61]	Animal models, in vivo (mice)	Neimann-Pick disease type C	NA	Storages of unesterified cholesterol and sphingolipids secondary to Neimann-Pick disease type C associated with increased CAMK1D expression, possibly as a function of lipid raft loss. Tissue expressions evaluated in deep cerebellar nuclei
Zhang et al (2022)[10]	Computational analysis, in silico	Non-alcoholic fatty liver disease	NA	CAMK1D identified as a 'hub' gene regulating nutrient metabolism and immune dysregulation, leading to non-alcoholic fatty liver disease
Schlauch et al (2022)[59]	GWAS, in vivo, human participants	Association between body mass index and adverse childhood events	Multi-ethnic cohort of 15 886 sequenced participants, with recalled information on adverse childhood events	Two CAMK1D variants (rs12777434 and rs71477259) showed the strongest gene per environment association between body mass index and adverse childhood events
Zhao et al (2010)[50]	Gene polymorphism, in vivo, human participants	Paediatric body mass index	Discovery cohort ($n = 3592$) and replication cohort ($n = 3592$)	CAMK1D (rs11257622) associated with paediatric body mass index in the discovery cohort, but **NOT** replicated in the additional cohort

(Continues)

TABLE 3 (Continued)

Author (year)	Study type	Disease/Phenotype	Sample size (human studies, ethnicity when available)	Main outcome
Rausch et al (2018)[48]	GWAS, in vivo, human participants	Non-alcoholic fatty liver disease	GWAS, in vivo. 243 minors under 18 years of age with non-alcoholic fatty liver disease. Hispanic sample	CAMK1D (rs17583338) associated with paediatric body mass index
Carayol et al (2020)[46]	Gene polymorphism, in vivo, human participants	Fasting insulin, HOMA-B, HOMA-IR	UK children at 5 years of age, followed through childhood ($n = 307$)	CAMK1D (rs12779790) associated with fasting insulin, HOMA-B and HOMA-IR. Same SNP also showed age-specific interactions with HOMA-B and HOMA-IR
Boesgaard et al (2009)[51]	Hyperinsulinemic euglycemic clamp, in vivo, human participants	Glucose stimulated insulin release and insulin sensitivity	Glucose stimulated insulin release ($n = 849$) and insulin sensitivity ($n = 596$). Assessed in non-diabetic offspring of Type 2 diabetic patients from European populations	CAMK1D (rs12779790) associated with elevated fasting serum insulin
Schrader et al (2021)[60]	Methylation study, in vivo, human participants	Statin therapy induced methylation changes	88 participants undergoing statin therapy, 110 controls Replication dataset: 58 participants undergoing statin therapy, 108 controls Swedish samples	Statin therapy associated with hypomethylation of CAMK1D
Lien et al (2022)[56]	Animal model, in vivo (mice)	Intrauterine growth restriction	NA	Diverging DNA methylation and associated gene expression changes in CAMK1D region
Alfaradhi et al (2010)[52]	Animal model, in vivo (mice)	Maternal obesity and associated traits in young, lean offspring	NA	CAMK1D levels were significantly elevated in the offspring of maternal obesity, possibly through post-transcription regulation by miRNA
Author (year)	**Study design**	**Disease**	**Sample size (human studies, ethnicity when available)**	**CAMK1D SNPs (along with statistical significance)**
EBI GWAS catalogue				
Christakoudi et al. (2021)[20]	GWAS, in vivo, human participants	Waist circumference adjusted for body mass index	219 872 women and 186 825 men with white British ancestry (from UK Biobank)	rs4748008 ($p = 3 \times 10^{-8}$)
Comuzzie et al. (2012)[21]	GWAS, in vivo, human participants	Childhood obesity and associated biological processes	815 children in a Hispanic population	rs4750211 (max respiratory ratio; $p = 6 \times 10^{-7}$), rs10906142 (fat mass change; $p = 1 \times 10^{-6}$), rs10906142 (fat mass deposition; $p = 1 \times 10^{-6}$), rs10906142 (energy storage; $p = 4 \times 10^{-6}$)

Note: In bold, non-significant results for CAMK1D associations with T2DM.

Abbreviations: EBI, European Bioinformatics Institute; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; T2DM, Type 2 diabetes mellitus.

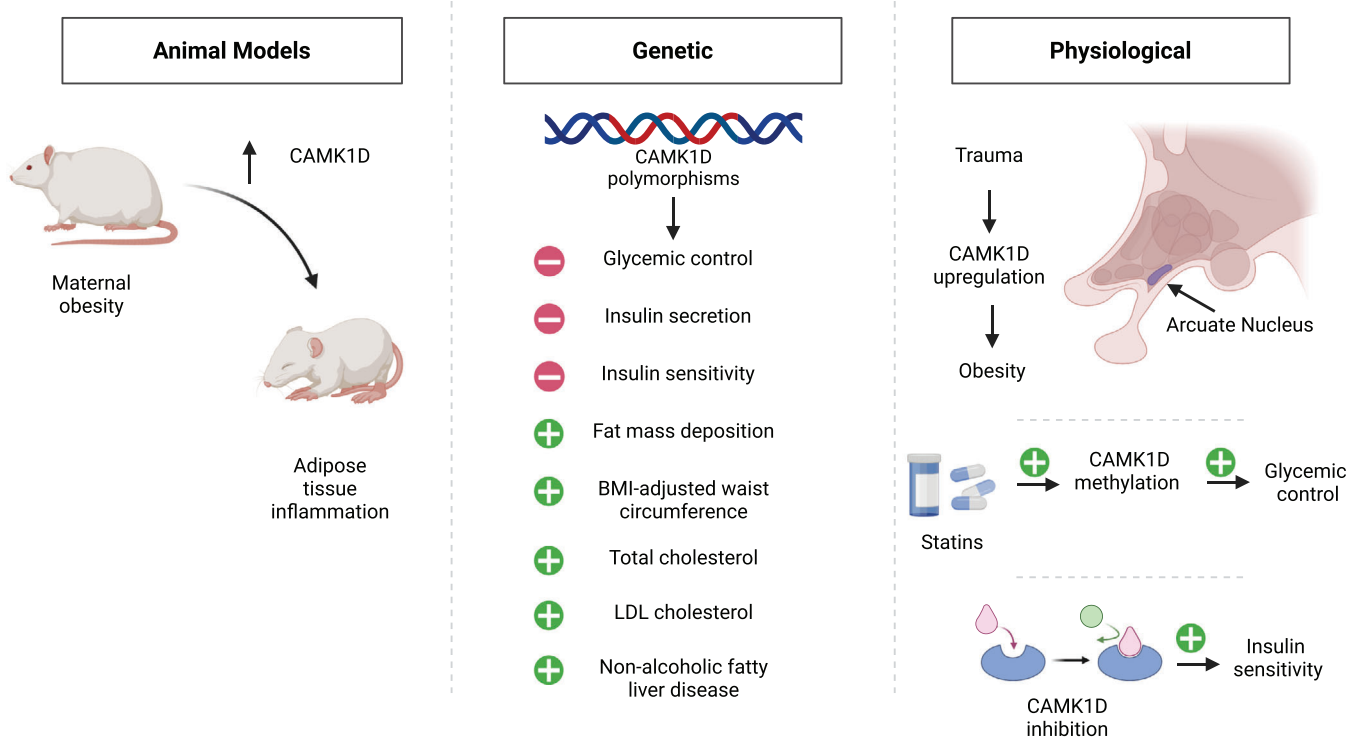

FIGURE 3 Graphical summary of results related to calcium/calmodulin-dependent protein kinase ID (CAMK1D) and metabolism. Evidence gathered in animal models, genetic studies and physiological studies shows CAMK1D as positively associated with maladaptive metabolic traits. Pharmacological studies show decreased synthesis/activity as associated with drugs known to ameliorate glycaemic control or insulin sensitivity, suggesting decreased CAMK1D activity/increased CAMK1D inhibition as a potential mechanism of action.

for CAMK1D's effects on metabolic traits, in particular for pancreatic beta cells,[46,55–58] possibly confounded by the concurrent regulation of specific factors related to energy availability.[56] For instance, different polymorphisms were linked with different responses to arginine, and specific polymorphisms significantly impacted on insulin secretion dynamics following food intake.[58] Interestingly, CAMK1D's polymorphisms were shown to mediate the effect of known risk factors (i.e., adverse childhood experiences and major traumatic events) on obesity,[59] with a mechanistic hypothesis given by the upregulation of CAMK1D in hypothalamic appetite nuclei in response to traumatic events (Figure 3).

Pharmacological studies showed that inhibiting CAMK1D restores insulin sensitivity, as evaluated by mouse models of diet-induced obesity (Figure 3).[40] Preliminary evidence surfaced suggesting that benefits associated with statin therapy may be at least partly associated with the induced methylation of specific genetic loci, including CAMK1D (Figure 3).[60] A successful overexpression of CAMK1D was achieved by pharmacological approaches, as evaluated by animal models. This overexpression was achieved by inhibiting other CAMK,[61] with yet unclear implications for future translational potentials, especially in humans.

3.3 | Food intake regulation

A recent study showed that within appetite nuclei in hypothalamic neurons CAMK1D signalling promotes ghrelin-mediated food intake.[11] To be noted, preliminary evidence suggests that CAMK1D's role in regulating food intake is conserved across species.[62] Interestingly, CAMK1D expression was previously shown to be downregulated in hypothalamic neurons (possibly including appetite-regulating nuclei) in response to high-fat diets (Figure 4),[63,64] although over-expressed in other regions within the brain and in a wider variety of tissues (Figure 4).[63]

Nonetheless, most evidence gathered on this topic derived from animal models (Table 4) or associations in animals between CAMK1D polymorphisms and feed intake.[62] For this reason, caution is warranted on the full translational potential of these results in humans. However, if confirmed by future studies, especially longitudinal studies conducted in humans, these results may better explain how and why CAMK1D exhibits tissue-specific effects. Indeed, included studies indicate that hypothalamic nuclei may differently respond to dietary habits, and diverging clinical conditions may exhibit hypo-activation of CAMK1D signalling in appetite nuclei,

TABLE 4 Calcium/calmodulin-dependent protein kinase ID (CAMK1D) and food intake regulation.

Author (year)	Study type	Disease/Phenotype	Sample size (human studies, ethnicity when available)	Main outcome
Published studies				
Vivot et al. (2023)[11]	Animal models, in vivo (mice)	CAMK1D knockout	NA	Knockout mice were resistant to ghrelin, gained less body weight and were protected against obesity as induced by high fat diets. CAMK1D deletion to achieve the same phenotype was necessary in agouti-related/NPY neurons, but deletion in POMC was not associated with the same outcomes. A mechanistic pathway through CREB phosphorylation and CREB-dependent expression of orexigenic neuropeptides (agouti/related protein, NPY) was proposed, as linking ghrelin effects through CAMK1D
Ho et al. (2013)[63]	Animal models, in vivo (mice)	Fasting, compared with normal or high fat diets	NA	CAMK1D expression is decreased in the central nervous system of animals exposed to fasting. CAMK1D expression in the liver downregulated by exposure to high glucose. Hence, metabolic factors regulate CAMK1D expression, according to tissue targets, with notable opposite directions of effect between the central nervous system and the periphery
Spinelli et al. (2024)[64]	Animal models, in vivo (mice)	High fat diets	NA	CAMK1D downregulated in the hippocampus of mice by high fat diet, possibly through differentially modulated miRNAs
Alboali et al. (2024)[62]	GWAS, animal model, in vivo (quail)	Feed intake regulation	NA	CAMK1D associated with feed intake
Maxwell et al. (2003)[45]	Animal models, in vivo (mice)	High cholesterol diet	NA	CAMK1D downregulated by high cholesterol diet. CAMK1D significantly upregulated in male and female SREBP-1a transgenic mice but unchanged in SREBP-2 transgenic mice. CAMK1D possibly regulated by sterol-regulatory element binding proteins, but **NOT** by liver X receptors

Note: In bold, non-significant results for CAMK1D associations with T2DM.

Abbreviations: GWAS, genome-wide association study; SNP, single nucleotide polymorphism; T2DM, Type 2 diabetes mellitus.

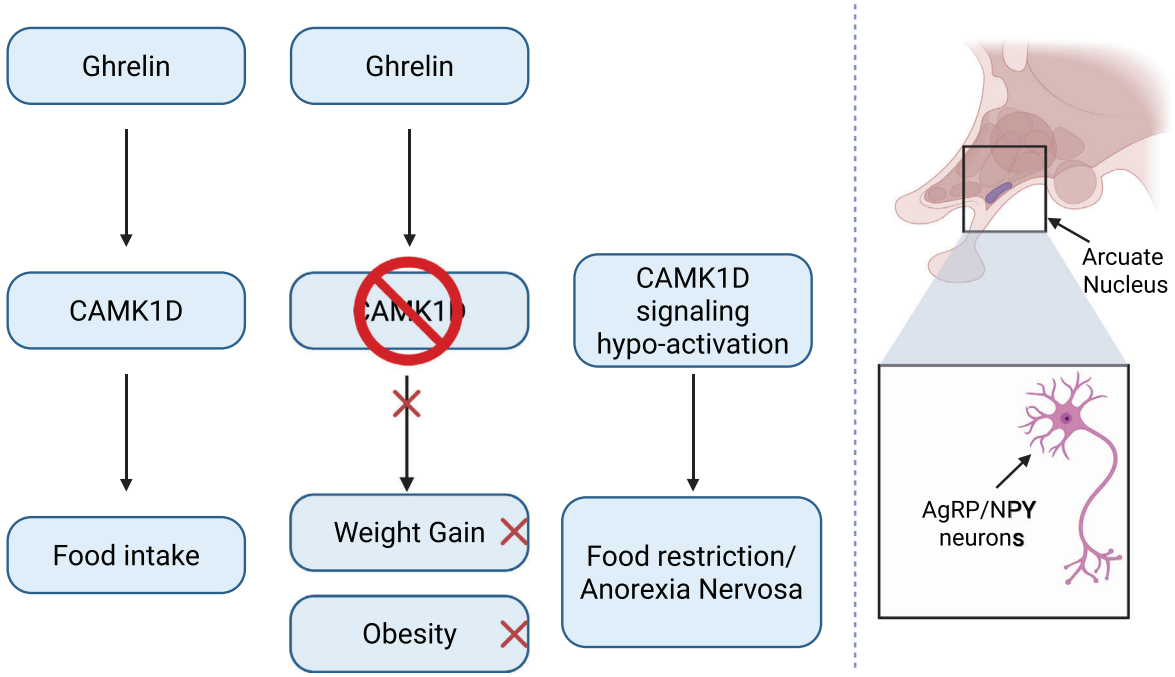

FIGURE 4 Graphical summary of results related to feeding behaviours and eating disorders. Promising evidence suggests calcium/calmodulin-dependent protein kinase ID (CAMK1D) as necessary for ghrelin-mediated food intake. In parallel, preliminary evidence suggests CAMK1D signalling hypoactivation as associated with food restriction, and, possibly, anorexia nervosa, paving the way for future translational studies as well as novel potential animal models for this psychiatric disorder.

TABLE 5 Calcium/calmodulin-dependent protein kinase ID (CAMK1D) and eating disorders.

Author (year)	Study design	Disease	Sample size (human studies, ethnicity when available)	CAMK1D SNPs (along with statistical significance)
EBI GWAS catalogue				
Wade et al. (2013)[6]	GWAS, in vivo, human participants	Four different phenotypes (anorexia nervosa, bulimia nervosa, purging via substances and maladaptive eating behaviours)	2564 female twins	rs75263140 ($p = 6 \times 10^{-6}$), rs10906233 ($p = 4 \times 10^{-6}$)

Note: In bold, non-significant results for CAMK1D associations with T2DM.
Abbreviations: EBI, European Bioinformatics Institute; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; T2DM, Type 2 diabetes mellitus.

although over-expressed in other tissues within the same clinical conditions.

3.4 | Eating disorders

A single study was retrieved, showing CAMK1D variants to be associated with disordered eating, more specifically anorexia nervosa (Table 5).[6] The relationship of this finding with subsequent evidence of CAMK1D's role in hypothalamic appetite regulation, metabolic control or immune dysregulation remains unexplored, notwithstanding, as previously summarized, the increasing amount of evidence suggesting a role for CAMK1D in regulating food intake (Figure 4)[65–68] and the concurrent consolidated evidence on metabolic and immune dysregulation in eating disorders.[4,65]

4 | LIMITATIONS AND FUTURE DIRECTIONS

A critical limitation of the current literature is the considerable heterogeneity of study designs and experimental

models. Many studies integrated into this review employed diverse methodologies—ranging from in vitro assays to in vivo animal models and population-based genetic analyses—which introduce variability that may hinder a wider generalizability of reported findings. Additionally, a number of investigations have used limited sample sizes, particularly in genetic association studies within diverse ethnic populations, raising concerns over statistical power.[33–36] Another constraint is the underrepresentation of longitudinal and interventional studies that could better elucidate the temporal and causal relationships between CAMK1D and diabetes or metabolic dysregulation. Furthermore, included studies often lacked standardization in the assessment of metabolic and behavioural outcomes, especially in the field of eating disorders, where specific diagnostic entities (i.e., bulimia nervosa) have been operatized as a behavioural spectrum,[6] possibly impeding the synthesis of a cohesive understanding of CAMK1D's role.

Nonetheless, common biases arising from collecting evidence in published literature, such as publication bias, may here be less pronounced. In fact, most studies did not aim to find a specific role for CAMK1D in target outcomes but rather employed a genome-wide approach[13–15,22,25–32] or multi-omic design.[10,42,53] Therefore, the tendency to retrieve positive findings over null results may have been attenuated.

Future research should prioritize the implementation of standardized protocols and larger, well-controlled clinical studies to validate the preliminary findings related to CAMK1D, especially for relatively neglected diagnostic entities, such as eating disorders (Table 5).[69] In-depth mechanistic studies using advanced genetic editing tools such as CRISPR/Cas9 and transcriptomic and proteomic profiling techniques seem warranted as to better delineate the downstream signalling networks and functional outcomes of CAMK1D modulation. Taken together, collected evidence may support the hypothesis that CAMK1D exhibits complex feedback mechanisms with upstream proteins,[44] sterol-binding regulatory sites[45] and tissue specific factors, as well as other proteins involved in the calcium/calmodulin pathway.[61]

The integration of longitudinal study designs will also be essential to clarify the temporal dynamics and potential causal pathways underlying CAMK1D-related metabolic disturbances, as well as better elucidating whether CAMK1D's association with diabetes may or may not be independent from the concurrent association with obesity-promoting traits.[37,52] Preliminary evidence is emerging on how treatments targeting diabetes, metabolic syndrome and weight loss may at least partly exert their effect through the inhibition of CAMKs.[60] Given the likely diverging effect in peripheral metabolism or central regulation of feeding behaviour,[11] future investigations may explore the therapeutic potential of CAMK1D inhibitors[40] or modulators in preclinical models of conditions of interest[61] while carefully delineating whether the observed effects are mediated centrally or peripherally.

5 | CONCLUSIONS

This systematic review highlights the emerging significance of CAMK1D as a multifaceted regulator in diabetes, metabolism and feeding behaviours. Evidence from genetic, molecular and preclinical studies supports its involvement in key pathways of insulin signalling and energy homeostasis. However, the heterogeneity of experimental models and the limited scope of current investigations underscore the need for larger scale, possibly longitudinal and clinical studies. Future research may focus on one hand on a better elucidation of molecular pathways linking increased CAMK1D expression to diabetes and obesity, while on the other on longitudinal analyses, as critical for validating CAMK1D as a potential molecular target for future translational purposes.

AUTHOR CONTRIBUTIONS

Livio Tarchi: Conceptualization; methodology; formal analysis; investigation; data curation; writing—original draft; writing—review and editing; visualization. **Annalisa Di Giacomo**: Formal analysis; investigation; data curation; writing—review and editing. **Lorenzo Bonacchi**: Conceptualization; methodology; investigation; writing—review and editing. **Andrea Di Santo**: Conceptualization, investigation; writing—review and editing. **Paolo Rovero**: Conceptualization, investigation; writing—review and editing; supervision. **Chiara Sassoli**: Conceptualization, investigation; writing—review and editing; supervision. **Rachele Garella**: Conceptualization, investigation; writing—review and editing. **Roberta Squecco**: Conceptualization, investigation; writing—review and editing; supervision. **Gianluca Villa**: Conceptualization, investigation; writing—review and editing; supervision. **Romina Nassini**: Conceptualization; investigation; writing—review and editing; resources; supervision. **Francesco De Logu**: Conceptualization; investigation; writing—review and editing; resources; supervision. **Tiziana Pisano**: Conceptualization; investigation; writing—review and editing; resources; supervision. **Valdo Ricca**: Conceptualization; investigation; supervision; funding acquisition; writing—review and editing; project administration. **Giovanni Castellini**: Conceptualization; investigation; validation; supervision; funding acquisition; writing—original draft; writing—review and editing; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request to the corresponding author.

ETHICS STATEMENT

Not applicable, as the current study did not involve human or animal subjects, as being based exclusively on published literature/information.

ORCID

Livio Tarchi https://orcid.org/0000-0002-9931-5621
Lorenzo Bonacchi https://orcid.org/0009-0004-9083-6086
Paolo Rovero https://orcid.org/0000-0001-9577-5228
Chiara Sassoli https://orcid.org/0000-0002-1337-0938
Rachele Garella https://orcid.org/0000-0003-3194-7603
Roberta Squecco https://orcid.org/0000-0002-6534-3675
Gianluca Villa https://orcid.org/0000-0003-4274-3593
Romina Nassini https://orcid.org/0000-0002-9223-8395
Francesco De Logu https://orcid.org/0000-0001-8360-6929
Tiziana Pisano https://orcid.org/0009-0007-5961-2588
Valdo Ricca https://orcid.org/0000-0002-9291-2124
Giovanni Castellini https://orcid.org/0000-0003-1265-491X

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