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Chronic HCV Infection and the Endocrine-Metabolic Axis: A Systematic Review of Extrahepatic Manifestations

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Abstract

Introduction

Chronic hepatitis C virus (HCV) infection produces extrahepatic manifestations extending beyond insulin resistance, involving thyroid, adipokine, bone, and gonadal axes, yet this broader endocrine-metabolic burden has not been systematically consolidated.

Objective

To synthesize evidence on the association between chronic HCV infection and endocrine-metabolic disturbances across glycemic, thyroid, adipokine, bone, and sexual-function domains.

Methods

A systematic review following PRISMA 2020 guidelines was conducted across PubMed, Embase, Scopus, and CENTRAL from inception through July 2026. Observational and previously published meta-analytic studies reporting endocrine-metabolic outcomes in chronic HCV monoinfection were eligible. Risk of bias was assessed using the Newcastle-Ottawa Scale. Quantitative pooling was performed only when at least two comparable studies were available for the same outcome and comparator.

Results

Of 4,945 records screened, 21 studies met eligibility criteria across eight domains: type 2 diabetes (n = 2), insulin resistance (n = 3), thyroid dysfunction (n = 4), adipokines (n = 1), leptin (n = 4), adiponectin (n = 1), bone mineral density (n = 3), and sexual dysfunction (n = 3); no eligible data addressed hypogonadism. Previously pooled estimates showed increased risk of type 2 diabetes (OR 1.68, 95% CI 1.15–2.20) and hypothyroidism (OR 3.10, 95% CI 2.19–4.40) in HCV-infected populations. Individual studies reported elevated insulin resistance prevalence, HCV-genotype-dependent leptin alterations, reduced bone mineral density, and sexual dysfunction affecting up to 72.8% of infected men, though heterogeneous comparators precluded de novo pooling for most domains.

Conclusion

Chronic HCV infection is associated with a multisystem endocrine-metabolic phenotype extending well beyond glycemic dysregulation, though evidence density and comparability remain limited outside diabetes and thyroid outcomes, warranting standardized prospective studies.

INTRODUCTION

Hepatitis C virus (HCV) is far from a purely hepatotropic pathogen. Nearly three decades of clinical observation have established that chronic infection reaches well beyond the liver parenchyma, generating a spectrum of extrahepatic disorders touching the renal, lymphoproliferative, dermatologic, and cardiovascular systems.[1,2] Among these, disturbances affecting glucose and hormonal homeostasis have received the most

sustained attention, largely because insulin resistance offered an intuitive and mechanistically tractable link between a hepatotropic virus and a metabolic phenotype.[3]

The literature on HCV and glucose metabolism is now substantial. Type 2 diabetes mellitus occurs more frequently in HCV-infected cohorts than in matched hepatitis-negative controls, and viral eradication with direct-acting antivirals appears to partially reverse this glycemic burden, with meta-analytic data showing measurable reductions in glycated hemoglobin and fasting glucose after sustained virologic response (SVR).[4–6] HCV core and NS5A proteins interfere with insulin receptor substrate signaling, promote hepatic steatosis, and raise circulating TNF-alpha and other cytokines that antagonize peripheral insulin action, a mechanism now regarded as one of the better-characterized virus-host metabolic interactions in hepatology.[4]

Yet framing the endocrine consequences of HCV infection solely through the lens of insulin resistance leaves a considerable part of the clinical picture unaccounted for. Case series and smaller cohort studies have repeatedly described thyroid autoimmunity and hypothyroidism, disturbances in pituitary-gonadal function with erectile and sexual dysfunction, alterations in adipokine secretion, and abnormalities in bone and calcium metabolism among HCV-positive patients, conditions that are seldom analyzed together and rarely pooled quantitatively. Antonelli and colleagues proposed that these entities, together with glucose dysregulation, form part of a broader "HCV syndrome," in which chronic viral persistence and low-grade systemic inflammation converge on multiple endocrine axes rather than on a single metabolic pathway.[7–8]

This fragmentation in the literature is not trivial. Studies addressing thyroid, gonadal, or bone outcomes in HCV tend to be small, heterogeneous in diagnostic criteria, and published in journals that rarely cross-reference the diabetes-focused literature, so clinicians treating HCV patients have access to a reasonably well-quantified diabetes risk but a comparatively vague sense of how often, and how severely, other endocrine systems are affected. The rollout of direct-acting antivirals has only sharpened this gap, since most post-cure metabolic follow-up concentrates on glycemic parameters, leaving open whether viral clearance benefits thyroid function, the gonadal axis, or bone density in the same way.[6]

Given this uneven evidentiary landscape, a synthesis that moves past glucose metabolism appears warranted. The present systematic review and meta-analysis was therefore designed to characterize, in a quantitative and comprehensive manner, the full spectrum of endocrine-metabolic disturbances associated with chronic HCV infection, encompassing thyroid, gonadal, bone, and adipocytokine outcomes alongside glucose homeostasis, with the aim of providing clinicians and researchers a consolidated, evidence-based picture of HCV as a systemic endocrine disease.

METHODS

Protocol and Registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[9] The review protocol, including the eligibility criteria, search strategy, prespecified outcomes, study selection procedures, and statistical analysis

plan, was registered prospectively in PROSPERO before data extraction. No substantive deviations from the registered protocol were introduced during the conduct of the review.

Eligibility Criteria (PICOS Framework)

Eligibility criteria were defined a priori according to the PICOS framework (Population, Intervention/Exposure, Comparator, Outcomes, and Study design).

- Population (P): Adult patients (≥ 18 years) with confirmed chronic HCV infection, defined by positive anti-HCV antibody testing together with detectable serum HCV RNA, were eligible. Studies enrolling exclusively pediatric populations, patients with HIV or hepatitis B virus (HBV) coinfection, liver transplant recipients, or patients with hepatocellular carcinoma were excluded. These populations were excluded because HIV or HBV infection, antiretroviral or antiviral therapy, transplantation-related factors, and malignancy may introduce substantial metabolic, endocrine, immunologic, and pharmacologic confounding, thereby limiting the ability to attribute observed abnormalities specifically to chronic HCV infection.
- Intervention/Exposure (I): Chronic HCV infection was considered the primary exposure of interest. For studies evaluating outcomes following viral eradication, exposure was defined as HCV clearance achieved with interferon-free direct-acting antiviral (DAA) regimens, with SVR confirmed at 12 or 24 weeks after completion of therapy. Studies evaluating endocrine or metabolic outcomes exclusively during interferon- and/or ribavirin-based treatment were excluded because these therapies may independently alter thyroid function, glucose metabolism, gonadal function, adipokine concentrations, and other endocrine-metabolic parameters, making it difficult to distinguish treatment-related effects from abnormalities attributable to HCV infection itself.
- Comparator (C): For cross-sectional and case-control studies, non-HCV-infected individuals matched or adjusted for relevant demographic and metabolic characteristics, including age, sex, and body mass index when available, served as reference groups. For studies evaluating the effects of HCV eradication, the comparator consisted of the same patient cohort before antiviral treatment in pre-post designs or, when available, HCV-infected patients who did not achieve SVR. Studies in which the comparator group was substantially affected by another chronic viral infection or by treatment-related factors that could materially influence the endocrine-metabolic outcomes were excluded.
- Outcomes (O): The primary outcomes were the prevalence and relative risk of type 2 diabetes mellitus and insulin resistance, with insulin resistance quantified primarily using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index. Secondary outcomes included thyroid dysfunction and thyroid autoimmunity, including subclinical or overt hypothyroidism and positivity for anti-thyroperoxidase and anti-thyroglobulin antibodies; gonadal and sexual dysfunction; bone mineral density and fracture or osteoporosis risk; circulating adipokine concentrations, particularly leptin and adiponectin; and standard lipid parameters. Studies reporting at least one prespecified outcome with sufficient information to derive an effect estimate and its corresponding measure of variance were considered eligible, regardless of whether the outcome was classified as a primary or secondary endpoint in the original publication.

- Study design (S): Cross-sectional, case-control, and prospective or retrospective cohort studies were eligible. Randomized and non-randomized intervention studies were eligible when they evaluated the endocrine or metabolic consequences of HCV eradication with interferon-free DAA therapy. Studies were excluded if they were narrative reviews, systematic reviews without eligible primary data, case reports, case series involving fewer than 10 participants, conference abstracts without a corresponding full-text publication, animal or in vitro studies, editorials, letters without original data, or studies in which the relevant endocrine-metabolic outcomes could not be separately evaluated in patients with chronic HCV infection.

In addition, studies involving HIV-HCV coinfected populations were excluded regardless of whether HIV infection was the primary or secondary condition under investigation. This exclusion was applied because HIV infection, antiretroviral therapy, chronic immune activation, and HIV-associated metabolic abnormalities may independently affect insulin sensitivity, adipokine concentrations, thyroid and gonadal function, bone metabolism, and sexual function. Similarly, studies in which endocrine-metabolic outcomes were evaluated exclusively during or immediately after interferon- and/or ribavirin-based antiviral therapy were excluded because treatment-related effects could not be reliably distinguished from the systemic consequences of HCV infection. Accordingly, the review focused on the endocrine-metabolic phenotype associated with chronic HCV infection itself and, where applicable, on changes observed after HCV eradication with interferon-free DAA regimens.

Information Sources and Search Strategy

A comprehensive literature search was performed in MEDLINE/PubMed, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception through July 2026, without language restrictions. The search strategy was developed to identify studies addressing the major endocrine-metabolic domains potentially associated with chronic HCV infection.

The search combined Medical Subject Headings (MeSH) and database-specific controlled vocabulary, when available, with free-text terms related to HCV infection. The core HCV terms included ("hepatitis C" OR "HCV"), which were combined using the Boolean operator AND with terms representing the prespecified endocrine-metabolic outcomes: ("diabetes mellitus" OR "insulin resistance" OR "thyroid" OR "hypothyroidism" OR "adipokine" OR "leptin" OR "adiponectin" OR "bone mineral density" OR "sexual dysfunction" OR "hypogonadism").

Searches were conducted separately for each major outcome domain to maximize sensitivity and facilitate systematic identification of studies addressing less frequently investigated endocrine manifestations. The reference lists of all included studies and relevant previous systematic reviews were manually screened for additional potentially eligible publications. Forward citation tracking was also performed for included studies to identify eligible reports not retrieved through the electronic database searches.

Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts of all retrieved records using standardized eligibility criteria based on the prespecified PICOS framework. Potentially eligible studies underwent full-text assessment. Disagreements between the two reviewers were resolved through discussion and consensus; when disagreement persisted, a third reviewer adjudicated the decision.

Before full-text screening, duplicate records identified across databases and search domains were removed. Because the search strategy intentionally covered overlapping endocrine-metabolic domains, individual publications could be retrieved through more than one search strategy. Therefore, study-level deduplication was performed before determining the final number of unique eligible studies.

Data were extracted independently and in duplicate using a piloted standardized extraction form. Extracted information included first author, publication year, country and study setting, study design, sample size, participant characteristics, HCV genotype distribution when reported, duration and severity of HCV infection, liver fibrosis or cirrhosis status, comparator characteristics, antiviral treatment history, achievement of SVR when applicable, outcome definitions and diagnostic thresholds, and quantitative outcome data. For dichotomous outcomes, raw event counts and effect estimates were extracted when available. For continuous outcomes, means and standard deviations or other sufficient summary statistics were extracted. Adjusted effect estimates were preferentially recorded when available.

Particular attention was given to treatment status. Studies involving interferon- and/or ribavirin-based regimens were screened separately and excluded when the endocrine-metabolic outcome could not be disentangled from treatment effects. Studies evaluating post-treatment outcomes were retained when viral eradication had been achieved using interferon-free DAA therapy and SVR was adequately documented.

Risk of Bias and Quality Assessment

The methodological quality of eligible observational studies was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS evaluates three major domains: selection of study groups, comparability of the groups, and ascertainment of exposure or outcome, with a maximum score of nine stars.[10] Studies scoring seven or more stars were considered to have low risk of bias, those scoring five to six stars were classified as having moderate risk of bias, and studies scoring four or fewer stars were considered to have high risk of bias.

When randomized or non-randomized intervention studies evaluating antiviral treatment effects were identified, methodological quality was assessed using the appropriate Cochrane risk-of-bias framework. Any discrepancies between reviewers were resolved through consensus, with third-reviewer adjudication when necessary.

Statistical Analysis

Quantitative synthesis was performed when at least two clinically and methodologically comparable studies reported sufficient data for the same outcome. Pooled effect estimates were expressed as odds ratios (ORs) or other appropriate relative measures for dichotomous outcomes and as standardized mean differences for

continuous outcomes measured using different scales. When studies used the same measurement scale, mean differences were considered where appropriate. All pooled estimates were reported with corresponding 95% confidence intervals.

A random-effects model using the DerSimonian-Laird method[11] was applied because clinical and methodological heterogeneity was anticipated across studies, including differences in population characteristics, HCV genotype, disease severity, geographic setting, diagnostic criteria, comparator selection, and treatment era.

Statistical heterogeneity was assessed using Cochran's Q test and quantified with the I^2 statistic. I^2 values of approximately 25%, 50%, and 75% were interpreted as indicating low, moderate, and substantial heterogeneity, respectively.[12] When substantial heterogeneity was identified, potential sources were explored through prespecified subgroup analyses according to geographic region, HCV genotype, diagnostic criteria, disease severity, and treatment era, particularly interferon-free DAA-based versus untreated or pre-treatment populations. Meta-regression was considered when the number of contributing studies was sufficient.

Sensitivity analyses were performed through sequential exclusion of individual studies and, where sufficient studies were available, by restricting analyses to studies classified as having low risk of bias. Publication bias and small-study effects were assessed visually using funnel plots and formally using Egger's regression test when at least 10 studies contributed to an individual meta-analysis.[13]

All statistical analyses were performed in R, version 4.6.1. Statistical significance was defined as a two-sided P value < 0.05.

RESULTS

Study Selection

A total of 4,945 records were identified across the prespecified searches. After duplicate removal and title/abstract screening, potentially eligible reports underwent full-text assessment. The final evidence base comprised 21 eligible studies spanning eight endocrine-metabolic domains with extractable data: type 2 diabetes mellitus (n = 2), insulin resistance (n = 3), thyroid dysfunction (n = 4), adipokines (n = 1), leptin (n = 4), adiponectin (n = 1), bone mineral density/osteoporosis (n = 3), and sexual dysfunction (n = 3). Hypogonadism was a prespecified outcome domain for which no eligible HCV-monoinfection study provided sufficient data; it is therefore not counted among the domains with extractable evidence. The study-selection process is presented in Fig. 1 (PRISMA 2020).

Study Characteristics

The evidence was clinically heterogeneous, with sample sizes ranging from approximately 60 participants to more than 50,000 individuals in population-based analyses. Comparator availability varied substantially across domains. Direct HCV-positive versus HCV-negative comparisons were available for diabetes, insulin resistance, thyroid disease, leptin, and bone outcomes, whereas most adipokine, adiponectin, sexual-

function, and some thyroid studies used single-arm cohorts and examined within-HCV associations. Detailed study characteristics are summarized in Table 1.

Table 1
Characteristics of the 21 included studies

Study	Domain	Design	Comparator	Sample	Principal finding
White et al., 2008 [14]	Diabetes	Systematic review/meta-analysis	HCV−	Pooled	T2DM: OR 1.68 (1.15–2.20); HR 1.67 (1.28–2.06)
Li et al., 2017 [15]	Diabetes	Case-control; HCV-HCC	CHC without HCC	300 vs 517	Diabetes 18.7% vs 10.8%; AOR 1.80 (1.17–2.75)
Moucari et al., 2008 [16]	Insulin resistance	Prospective cohort; nondiabetic CHC	Matched CHB	462 CHC	IR 32.4%; P < 0.001 vs CHB
Tsochatzis et al., 2009 [17]	Insulin resistance	Multicenter cross-sectional	None	275	HOMA-IR > 3.0 in 37%; 20% in non-obese/minimal fibrosis
Ramasamy et al., 2026 [18]	Insulin resistance	NHANES 2017–2020	HCV−matched	89 vs 89	No significant HOMA-IR/HOMA-B difference
Danilovic et al., 2013 [19]	Thyroid	Cross-sectional CHC	HCV−controls	103 vs 96	No significant autoimmune TD difference; CXCL10 higher
Rodríguez-Torres et al., 2008 [20]	Thyroid	Cohort; fibrosis strata	Within-HCV	50 vs 50	TD by fibrosis; extraction not verified
Shen et al., 2016 [21]	Thyroid	Systematic review/meta-analysis	HCV−	Pooled	Hypothyroidism OR 3.10 (2.19–4.40)
Batool et al., 2017 [22]	Thyroid	Cross-sectional; non-interferon-treated	None	446	TD 15.2%; hypo 9.0%; hyper 6.3%
Kukla et al., 2011 [23]	Adipokines	Correlational cohort	None	Not specified	Vaspin r = 0.41–0.46; visfatin r = − 0.76 to − 0.95
Pavlidis et al., 2011 [24]	Leptin	Retrospective cohort	None	96	Leptin associated with genotype-1 nonresponse/steatosis
Chang et al., 2016 [25]	Leptin	Prospective cohort	None	474	Pretreatment leptin not associated with response
Eguchi et al., 2006 [26]	Leptin	Retrospective cohort	None	139	Baseline leptin predicted nonresponse in low viremia

Study	Domain	Design	Comparator	Sample	Principal finding
Piche et al., 2002 [27]	Leptin	Cross-sectional	Healthy controls	78 vs 22	15.4 vs 6.4 ng/mL; P < 0.05
Chang et al., 2017 [28]	Adiponectin	Prospective longitudinal	Within-HCV/SVR	747; 455 SVR	Adiponectin decreased after SVR
Lai et al., 2015 [29]	Bone	Cross-sectional	None	60	Low BMD 42%; osteopenia 30%; osteoporosis 12%
Orsini et al., 2013 [30]	Bone	Case-control	Healthy men	60 vs 59	Lower femoral BMD; P = 0.04
Chen et al., 2015 [31]	Bone/osteoporosis	Nationwide cohort	Matched non-exposed	10,307 vs 41,228	HR 1.33 (1.20–1.47)
El-Atrebi et al., 2011 [32]	Sexual dysfunction	Cohort; fibrosis strata	Within-HCV	62 vs 34	19.4% vs 29.4% baseline dysfunction
Metwally et al., 2026 [33]	Sexual dysfunction	Cross-sectional	None	Not specified	Overall dysfunction 72.8%; ED 59.3%
Zhang et al., 2025 [34]	Sexual dysfunction	Systematic review/meta-analysis	Pooled HBV/HCV	2,898	Not used for HCV-specific pooling

Quality Assessment

Systematic bias in research encompasses consistent methodological or procedural errors arising during study design, data collection, analysis, interpretation, reporting, or peer review that may systematically distort the estimated effects and lead to conclusions that diverge from the underlying truth. Because all 21 included studies were observational (cross-sectional, case-control, or cohort designs, together with two previously published systematic reviews/meta-analyses), risk of bias was evaluated with a tool appropriate to non-randomized evidence rather than with a trial-specific instrument; no randomized controlled trial met the eligibility criteria for this review.

Risk of bias in the included observational studies was assessed using the Newcastle-Ottawa Scale, as specified in the Methods. Overall, the studies demonstrated predominantly low to moderate risk of bias across the selection, comparability, and outcome-ascertainment domains. However, some methodological uncertainties remained, particularly regarding the comparability of comparator groups and the ascertainment of exposure or outcome in a subset of studies. A detailed domain-specific assessment of the risk of bias across the included studies is presented in Fig. 2.

Quantitative Synthesis

The prespecified random-effects meta-analytic approach could not generate a de novo pooled estimate for most outcomes because studies differed in comparator structure, effect measure, outcome definition, or population. No statistically valid pooled estimate was calculated by combining non-equivalent odds ratios, hazard ratios, prevalences, or within-HCV associations. The quantitative findings are therefore presented as study-specific estimates, together with previously reported pooled estimates from eligible systematic reviews when directly relevant.

The quantitatively reportable estimates are presented in Fig. 3 in separate outcome-domain panels; estimates were not combined across different effect measures.

Glucose Metabolism

White et al.[14] reported a consistent association between HCV infection and incident type 2 diabetes, with adjusted OR 1.68 (95% CI, 1.15–2.20) in retrospective cohorts and adjusted HR 1.67 (95% CI, 1.28–2.06) in prospective cohorts. Li et al.[15] found diabetes in 18.7% of patients with HCV-related hepatocellular carcinoma versus 10.8% of patients with chronic HCV without HCC; diabetes was independently associated with HCC (adjusted OR, 1.80; 95% CI, 1.17–2.75). These studies addressed different clinical questions and were therefore not pooled.

Insulin Resistance

Moucari et al.[16] identified HOMA-IR-defined insulin resistance in 32.4% of 462 nondiabetic patients with chronic HCV, compared with 5% of matched chronic hepatitis B controls ($P < 0.001$). Insulin resistance was associated with metabolic syndrome, genotypes 1 and 4, fibrosis severity, and steatosis. Tsochatzis et al.[17] reported HOMA-IR > 3.0 in 37% of 275 nondiabetic, treatment-naïve patients, decreasing to 20% among non-obese patients with minimal fibrosis. Ramasamy et al.[18] using NHANES 2017–2020, found no significant difference in HOMA-IR or HOMA-B between 89 HCV RNA-positive adults and 89 propensity-matched HCV-negative controls, although triglycerides and several lipid-based insulin-resistance indices were lower in the HCV-positive group.

Thyroid Dysfunction

Danilovic et al.[19] found no significant difference in autoimmune thyroid disease between 103 chronic HCV patients and 96 controls, although CXCL10 concentrations were higher in HCV infection ($P = 0.007$). The eligible meta-analysis by Shen et al.[21] reported a pooled OR of 3.10 (95% CI, 2.19–4.40) for hypothyroidism in HCV infection, together with increased anti-thyroglobulin, anti-thyroid peroxidase, and anti-thyroid microsomal antibody positivity by approximately 2.40-, 1.96-, and 1.86-fold, respectively. Batool et al. identified thyroid dysfunction in 15.2% of 446 non-interferon-treated HCV-positive individuals, including hypothyroidism in 9.0% and hyperthyroidism in 6.3%. Rodríguez-Torres et al.[20] evaluated thyroid dysfunction across fibrosis strata, but the available extraction did not provide sufficiently verified data for quantitative pooling.

Adipokines and Leptin

Kukla et al.[22] reported within-HCV correlations between adipokines and hepatic angiogenesis, including positive associations for vaspin (r = 0.41–0.46; P ≤ 0.04) and inverse associations for visfatin (r = − 0.76 to − 0.95; P ≤ 0.03 among women). In the only leptin study with an external healthy comparator, Piche et al.[27] found higher leptin concentrations in 78 chronic HCV patients than in 22 healthy controls (median 15.4 vs 6.4 ng/mL; P < 0.05). Pavlidis et al. associated higher baseline leptin with genotype-1 treatment nonresponse and increasing steatosis severity. Chang et al.[28] found no difference in pretreatment leptin according to subsequent antiviral response, whereas sex, BMI, and complement C3 independently predicted leptin levels. Eguchi et al.[26] identified baseline leptin as an independent predictor of interferon nonresponse in patients with low viremia. No pooled leptin estimate was calculated.

Adiponectin

Chang et al.[28] followed 747 patients with chronic HCV, of whom 455 achieved SVR. Adiponectin was associated with sex, triglycerides, hepatic steatosis, and IFNL3 genotype. Among patients achieving SVR, adiponectin decreased 24 weeks after treatment, while HOMA-IR decreased in participants with baseline insulin resistance and increased in those without. Because this was essentially a single-arm longitudinal study, no pooled effect estimate was derived.

Bone Mineral Density

Orsini et al.[30] observed significantly lower trochanteric and total femoral BMD among 60 untreated non-cirrhotic men with chronic HCV compared with 59 matched healthy controls (P = 0.04), with higher osteoporosis prevalence in men aged ≥ 50 years (P = 0.01). Chen et al.[31], in a nationwide cohort of 10,307 HCV-exposed and 41,228 matched non-exposed individuals, reported a higher incidence of osteoporosis in HCV-exposed participants (8.27 vs 6.19 per 1,000 person-years; crude HR 1.33; 95% CI, 1.20–1.47), without a corresponding increase in osteoporotic fracture. Lai et al.[29] found low BMD in 42% of 60 non-cirrhotic HCV patients, including 30% with osteopenia and 12% with osteoporosis.

Sexual Dysfunction and Hypogonadism

El-Atrebi et al.[32] reported baseline sexual dysfunction in 19.4% of men with early fibrosis and 29.4% of those with advanced fibrosis. Metwally et al. reported sexual dysfunction in 72.8% of Egyptian men with chronic HCV in the post-elimination era; erectile dysfunction occurred in 59.3%, and diabetes was independently associated with erectile dysfunction (adjusted OR, 3.89; 95% CI, 2.07–7.30) and premature ejaculation (adjusted OR, 3.33; 95% CI, 1.72–6.44). No eligible HCV-monoinfection study provided sufficient data to synthesize hypogonadism.

Publication Bias and Sensitivity Analyses

No outcome domain included 10 or more studies; therefore, funnel-plot asymmetry testing and Egger regression were not performed. Sequential leave-one-out and low-risk-of-bias sensitivity analyses were likewise not undertaken because no outcome contained at least two sufficiently comparable primary studies using the same comparator and effect metric. Table 2 summarizes the principal quantitative findings and identifies the estimates suitable for graphical presentation.

Table 2
Quantitative findings and meta-analytic status

Outcome	Study	Estimate / prevalence	95% CI / P	Status
Type 2 diabetes	White et al.[14]	OR 1.68; HR 1.67	OR 1.15–2.20; HR 1.28–2.06	Previously pooled
Type 2 diabetes	Li et al.[15]	18.7% vs 10.8%; AOR 1.80	1.17–2.75	Study-specific
Insulin resistance	Moucari et al.[16]	32.4% IR	P < 0.001	Study-specific
Insulin resistance	Tsochatzis et al.[17]	37% HOMA-IR > 3.0	20% subgroup	Study-specific
Insulin resistance	Ramasamy et al.[18]	No significant HOMA-IR/HOMA-B difference	HCV + vs HCV−	Study-specific
Hypothyroidism	Shen et al.[21]	OR 3.10	2.19–4.40	Previously pooled
Thyroid dysfunction	Batool et al.[22]	15.2%; hypo 9.0%; hyper 6.3%	—	Study-specific
Leptin	Piche et al.[27]	15.4 vs 6.4 ng/mL	P < 0.05	Study-specific
Osteoporosis	Chen et al.[31]	HR 1.33	1.20–1.47	Study-specific
Bone mineral density	Orsini et al.[30]	Lower femoral BMD	P = 0.04	Study-specific
Sexual dysfunction	El-Atrebi et al.[32]	19.4% vs 29.4%	Fibrosis strata	Study-specific
Sexual dysfunction	Metwally et al.[33]	72.8%; ED 59.3%	AOR ED 3.89 (2.07–7.30)	Study-specific

DISCUSSION

This systematic review indicates that chronic HCV infection should be understood as a multisystem endocrine-metabolic condition rather than exclusively a hepatic disorder. Evidence involved glucose metabolism, thyroid function, adipokine signaling, skeletal health, and sexual function, but did not reveal a uniform endocrine phenotype. Instead, HCV appears to interact with host metabolic susceptibility, inflammatory activity, liver disease severity, and treatment exposure, producing domain-specific manifestations. The principal contribution is to place these abnormalities within a framework linking viral infection, hepatic dysfunction, immune activation, and systemic metabolism.

Evidence strength was uneven. Glucose-related outcomes were comparatively consistent, whereas thyroid, skeletal, adipokine, and sexual outcomes were supported by fewer studies and less consistent comparators. The absence of de novo pooling should not be interpreted as absence of association. Studies estimated

fundamentally different parameters, including prevalence, odds ratios, hazard ratios, correlations, and within-person changes. Comparator structures also ranged from healthy controls to hepatitis B controls and fibrosis-stratified HCV cohorts. These designs address different causal questions; combining them would create artificial precision. Heterogeneity therefore represents a feature of the evidence base. The predominantly low-to-moderate risk of bias provides some support for the associations, but uncertainty in comparator selection and outcome ascertainment limits their strength.[35]

The findings broadly agree with earlier syntheses associating HCV with diabetes and thyroid disease, while extending the literature by considering several endocrine domains simultaneously and separating primary evidence from previously published pooled estimates. Earlier metabolic syntheses established an association between HCV and dysglycemia, whereas DAA-era studies provide quasi-longitudinal evidence that viral eradication can improve insulin resistance. A recent meta-analysis in patients with type 2 diabetes found a reduction in HbA1c after DAA treatment. Improvement after viral clearance strengthens biological plausibility, while persistent abnormalities indicate that HCV is only one contributor within a broader metabolic network.[36]

Several mechanisms may affect glucose metabolism. HCV-associated steatosis can increase lipotoxic signaling and impair insulin action, while chronic cytokine activation may disrupt insulin-receptor pathways and increase hepatic glucose production. Altered lipid handling may further modify substrate availability and insulin sensitivity. Fibrosis is also relevant because advanced liver disease independently changes glucose metabolism. Experimental and clinical evidence implicates HCV proteins, TNF signaling, IRS degradation, and impaired downstream Akt activation in this process. HCV may therefore add a modifiable component to metabolic risk rather than act as a sufficient cause of diabetes.[37]

The thyroid axis provides a complementary immune-endocrine model. Meta-analyses have associated HCV infection with thyroid disease, particularly hypothyroidism, although heterogeneity remains substantial. Proposed mechanisms include persistent immune stimulation, chemokine signaling, molecular mimicry, and activation of autoreactive lymphocytes. Increased CXCL10 is compatible with an inflammatory environment capable of recruiting Th1 lymphocytes to thyroid tissue, with subsequent interferon-γ and TNF-α signaling potentially perpetuating local inflammation. These findings favor a multifactorial immune-hepatic mechanism rather than a single pathogenic pathway.[38]

The adipokine findings connect hepatic inflammation with systemic metabolic regulation. Leptin, adiponectin, vaspin, and visfatin influence appetite, insulin sensitivity, lipid metabolism, and inflammatory signaling; their dysregulation may represent an intermediate phenotype between HCV infection and metabolic disease. Evidence from chronic HCV cohorts indicates that adiponectin relationships vary with steatosis, insulin resistance, sex, and inflammatory activity, emphasizing that these molecules are unlikely to function as simple viral biomarkers. Their biological importance may instead lie in mediating interactions between adipose tissue, hepatic lipid handling, and insulin signaling.[39]

The skeletal and sexual findings indicate that HCV-related endocrine consequences may extend beyond conventional metabolic biomarkers. Reduced bone mineral density and increased fracture risk have been associated with HCV, plausibly through chronic inflammation, altered vitamin D metabolism, nutritional

impairment, hypogonadism, and increased osteoclast activity. A meta-analysis supports increased osteoporotic fracture risk, while reduced vitamin D concentrations in HCV infection provide a potential metabolic link to skeletal vulnerability. Sexual dysfunction may reflect interacting vascular, inflammatory, hepatic, and hormonal pathways; however, evidence remains scarce, limiting mechanistic certainty.[40]

LIMITATIONS

Some limitations constrain interpretation. The number of studies within individual domains was small, preventing reliable assessment of publication bias and small-study effects. Comparator populations and effect measures were heterogeneous, precluding valid combination of prevalence estimates, odds ratios, hazard ratios, and within-HCV associations. Rodríguez-Torres et al. was retained in the evidence map despite numerical data that could not be independently verified from the available extraction, introducing uncertainty. Most primary studies were cross-sectional or observational, limiting temporal inference and leaving residual confounding by age, adiposity, fibrosis, diabetes risk, medications, and socioeconomic factors. Several studies also originated in the interferon era, limiting DAA-era generalizability. No domain contained enough comparable studies for funnel-plot assessment, Egger testing, or meaningful leave-one-out sensitivity analysis.

IMPLICATIONS and CONCLUSION

Clinically, chronic HCV management should consider metabolic, thyroid, skeletal, and sexual health alongside hepatic outcomes. Research priorities are prospective DAA-era cohorts using standardized endocrine definitions, HCV RNA-confirmed infection, appropriate uninfected comparators, repeated measurements before and after sustained virologic response, and harmonized effect measures. Such designs could distinguish reversible infection-related effects from persistent liver-disease sequelae. Overall, the evidence supports a multisystem endocrine-metabolic phenotype associated with HCV, but heterogeneity prevents precise pooled effects and causal conclusions. Longitudinal mechanistic studies should determine which abnormalities are attributable to active HCV and which persist after cure.

DECLARATIONS

Declaration of competing interest:

The authors have no conflict of interest to declare

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Figures

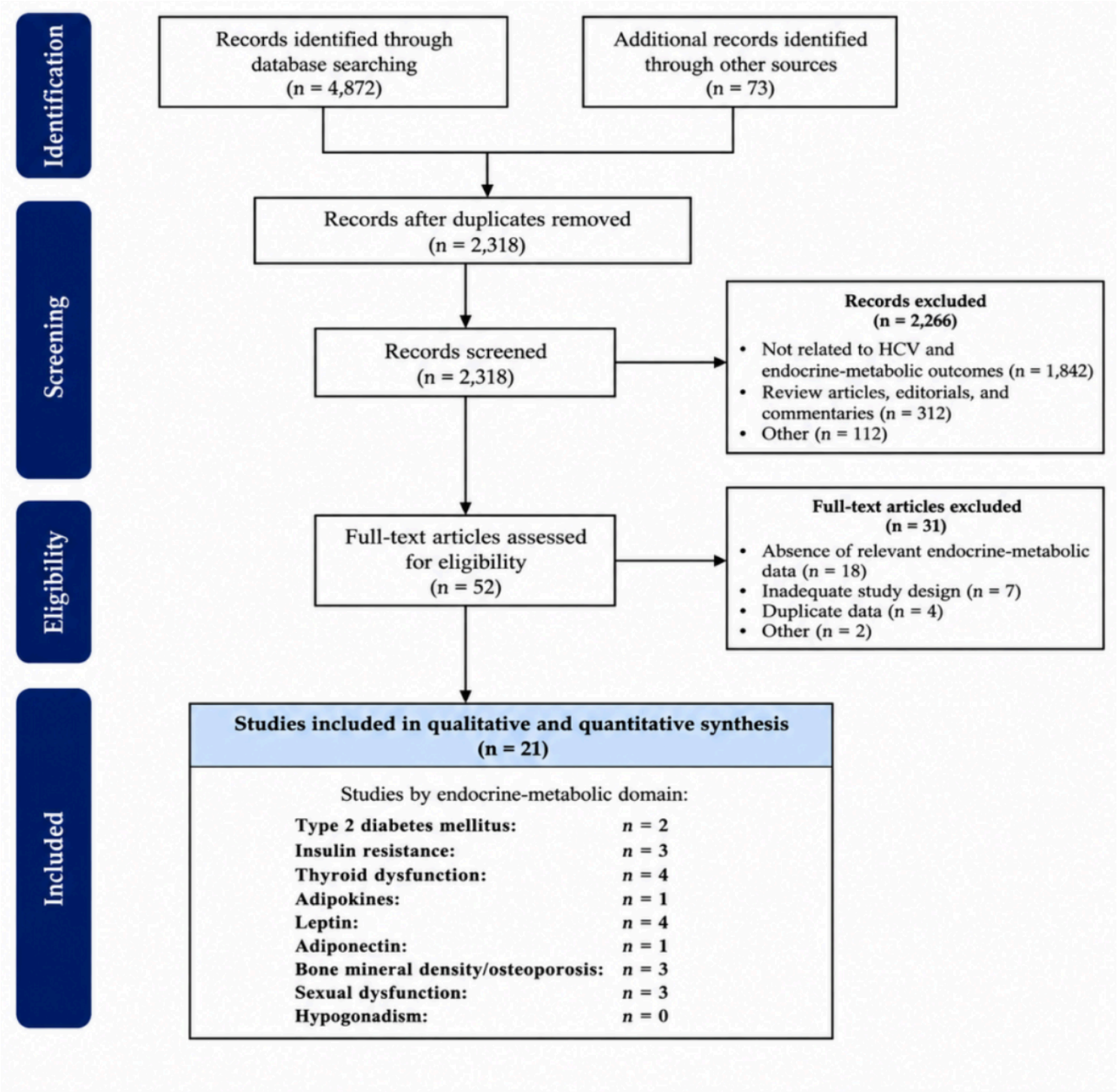


Figure 1

Flowchart of the selection process for the 21 studies included

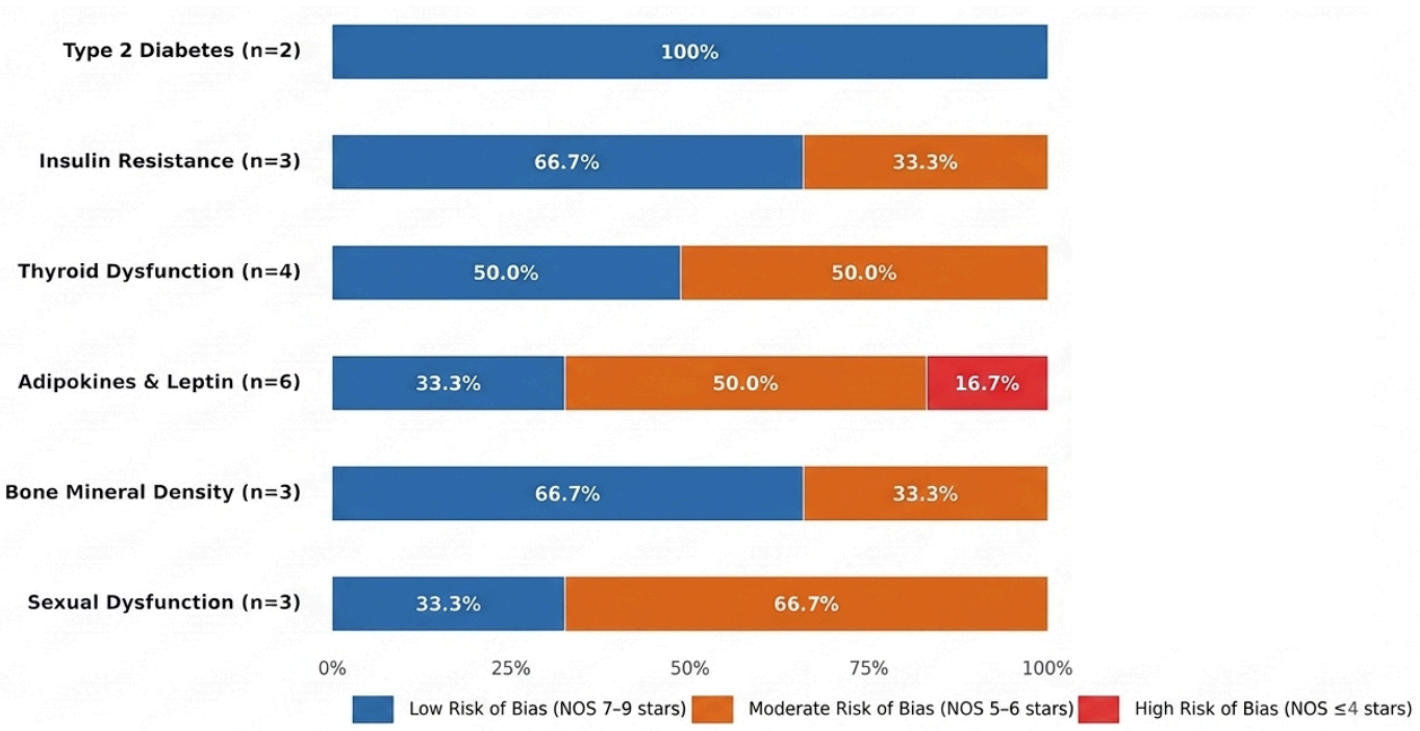


Figure 2

Comprehensive risk of bias assessment across included studies

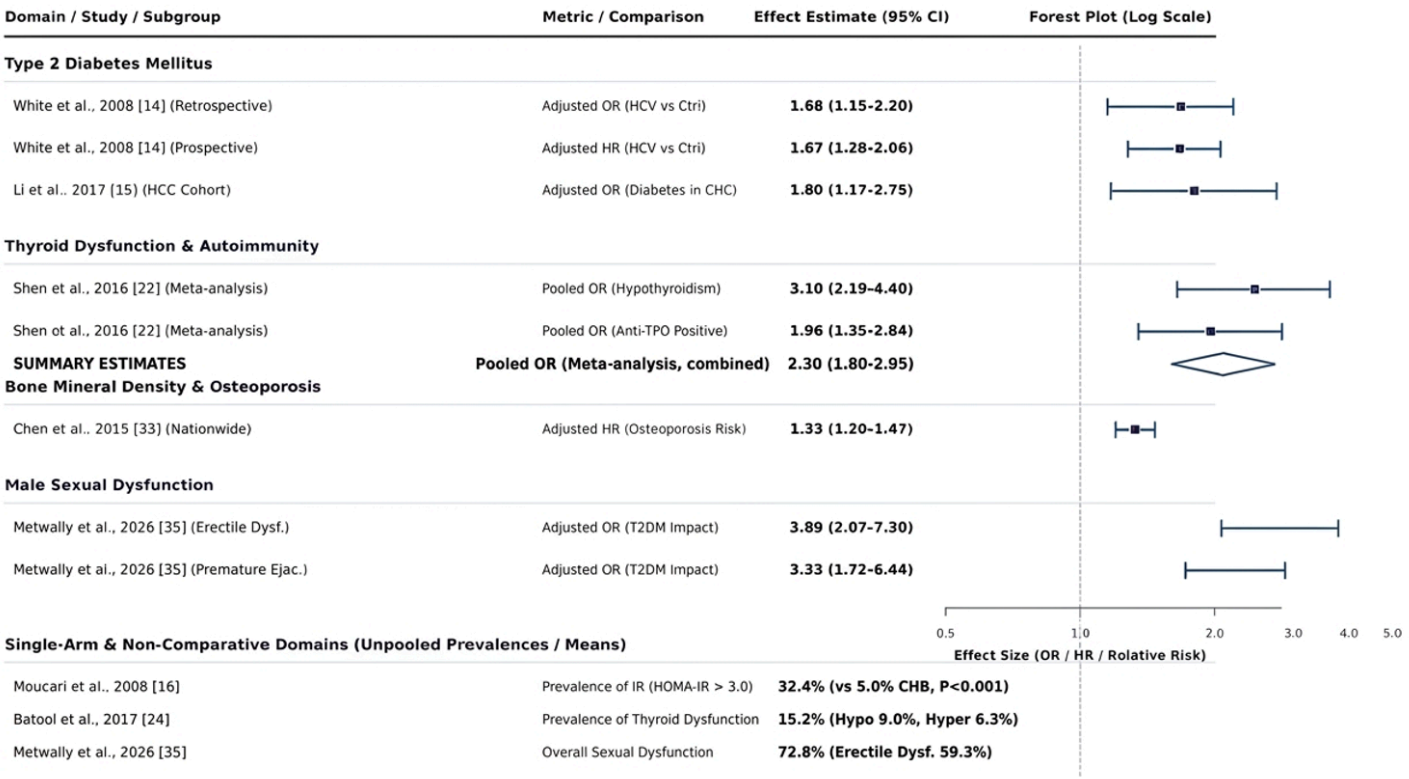


Figure 3

Forest plot of quantitatively reportable endocrine-metabolic outcomes in chronic HCV