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Is routine laboratory testing in healthy young patients taking isotretinoin necessary – a critically appraised topic

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Abstract

Clinical question/scenario

Is monitoring of liver function, lipids and full blood count necessary in healthy people taking isotretinoin?

Background

Routine blood testing was recommended in the original licence for Roaccutane™ in 1983. In recent years, less frequent monitoring has been suggested by various authors.

Data sources

We performed four individual systematic searches of MEDLINE, via PUBMED, database from origin to May 2, 2021, supplemented by a hand search of all references in identified papers.

Study selection

Inclusion criteria were: any description of clinical symptoms, laboratory abnormalities and/or physical findings, and any paper that explicitly described the patients as asymptomatic, during treatment with oral isotretinoin.

Data extraction

Two independent reviewers (J.A. and D.J.) assessed articles for eligibility of inclusion. Evaluation of the data was done also by two of the authors (A.A., D.J., and JA) for each section, with the aim to use the presented evidence including guidelines, databases, case series, case reports, cohort studies and randomized clinical trials to delineate the clinical presentation and frequency of adverse events which might be amenable to laboratory monitoring.

Results / Identified evidence

We identified 406 papers in our searches and reviewed 127 papers in four sections. In summary reported adverse events were very rare (less than 1 in 10,000) and either idiosyncratic or not preventable by monitoring, were accompanied by symptoms, or occurred in identifiable predisposed individuals that may benefit from monitoring because of pre-existing conditions.

Discussion and recommendation for clinical care

We could not find evidence to support the benefit of monitoring to detect adverse events. We suggest that in healthy young people laboratory monitoring for oral isotretinoin is unnecessary and risks detecting non-serious biochemical abnormalities. However, we recognise that new information about adverse events may change that recommendation.

Clinical Question

Is monitoring of liver function, lipids and full blood count useful to detect serious adverse events in healthy people taking oral isotretinoin?

Clinical scenario

A 16-year-old healthy boy with no significant previous illnesses and severe treatment-resistant acne attends the dermatology clinic. He does not want to miss school and would like to forgo blood tests. Based on the available evidence can he be treated safely?

Background

Isotretinoin is a valuable acne treatment but remains controversial. It is the only treatment that can arrest severe acne permanently but causes a high frequency of birth defects or spontaneous abortions. It causes predictable elevation of liver function tests (see below), and blood lipid elevations in ~20%, and very rarely idiopathic pancreatitis. The British National Formulary (BNF) re-enforces concerns; "Isotretinoin is a toxic drug that should be prescribed only by, or under the supervision of, a consultant dermatologist."[1] Isotretinoin is the only generally toxic medication i.e. not cardiotoxic, ototoxic etc in the BNF, with the exception of pentamine which is classified as "a potentially toxic drug."[1] Even cyclophosphamide, a medication with a high risk side effect profile, does not have a similar warning.

Mitigation of adverse events is of the highest importance. The FDA mandates a complex, Risk Evaluation and Mitigation Strategy (REMS) that has reduced the number of pregnancies on the drug by a third.[2]

In young healthy patients, expected changes of laboratory values can be challenging to interpret, and there is a large body of conflicting evidence.[3-6] Blood monitoring is not even mentioned in the recent NICE guidelines.[7]

We wanted to investigate the clinical presentation of adverse events to understand whether laboratory monitoring prevents, or detects adverse events early. We systematically searched and summarized the literature of evidence that laboratory monitoring is helpful; when it is helpful; and how often it should be done.

Aim of this Critically Appraised Topic

To evaluate whether routine blood testing for liver function, lipids, full blood count, thyroid function tests and muscle enzymes are needed in healthy people taking a course of isotretinoin for acne in order to prevent and act on adverse events. The approach is toxicological in that the observed adverse events are analysed clinically to assess whether laboratory monitoring can potentially prevent them, or whether early detection would lead to a change in outcome.

METHODOLOGY

IDENTIFICATION OF BLOOD TESTS TO BE EVALUATED

The list of blood tests that are part of this critically appraised topic (CAT) was based on discussions among the authors and BJD editorial teams.

LITERATURE SEARCH

We limited the list of laboratory tests discussed in this CAT based on the package insert,[4] the BNF,[1] the British Association of Dermatologists' (BAD) guidelines,[5] personal discussion and available literature. After discussion amongst the authors we focused on Full Blood Count, Thyroid tests, Liver enzymes, Muscle enzymes and Triglyceride checks[8]. These tests go beyond the package inserts and usual recommendations. We performed four individual systematic searches of MEDLINE, via PUBMED, databases from origin to May 2, 2021, supplemented by a hand search of all references in identified papers. The results for Triglycerides were summarized based on a previous systematic review.[9] The searches with results and search terms are outlined in detail in appendix 1. All search results were independently selected for review by two reviewers (DNJ, JA). Any differences of opinion were resolved by personal discussion.

SELECTION CRITERIA

We screened articles based on their abstract and title. All relevant papers were reviewed in full text. Inclusion criteria were: any description of clinical symptoms, laboratory abnormalities and/or physical findings, and any paper that explicitly described the patients as asymptomatic, during treatment with oral isotretinoin. No restrictions were imposed on publication date, study design, or language (excepting two papers in Hungarian and Hebrew where no translation could be found). Duplicate reports and articles that contained only abstracts were excluded. (Diagram 1-4).

DATA EXTRACTION

A predetermined data form was used to extract information that included study design, sample size, and events with conclusions reported in the article.

CLINICAL APPROACH

Analysis of rare events has to be clinical since statistical methods are not useful for exceedingly rare events. As a consequence case reports remain the basis for a majority of relevant safety decisions by regulatory agencies.[10-12] Monitoring has to be clinically sensible.

Drugs are removed from the market when the incidence of drug induced liver injury (DILI) rises above 1 in 10.000.[13] Based on a simple rule,[14] a series of about 30.000 patients without event would be needed to show that the risk of DILI is below 1 in 10.000. Such large series are rare, so individual case reports have to be analyzed. This was done for terbinafine, where the incidence of DILI is around 1 per 50.000 – 120.000 prescriptions, and 69 cases were analyzed.[15] Based on clinical presentation, drug characteristics, and reported frequency, an analysis of causal attribution and utility of monitoring can be made. In this way, our approach seeks to mimic that of agencies such as the FDA.

LIVER FUNCTION

Current Recommendations:

BNF + EMC monitoring advice - Measure hepatic function before treatment, 1 month after starting and then every 3 months (reduce dose or discontinue if transaminase persistently raised).[1,4] The BAD guidelines recommend testing after 4-6 weeks, and then every 3 months.[5]

Evidence Found:

Our search identified 204 papers of which 61 papers were selected for review, two additional papers were found in the references, two papers were excluded (Diagram 1 and Table 1).

It is clear that isotretinoin leads to an elevation of liver enzymes in a large proportion of patients. We identified only one poorly documented case of "probable" DILI,[16] based on the Council for the international organization of medical sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) criteria.[17,18] The CIOMS/RUCAM criteria are meant to assess causality in cases of hepatotoxicity. However, the paper does not give enough information to confirm "probable" causation, only "possible" causality. On day 70 of an isotretinoin course an asymptomatic female patient presented with elevated LFTs and bilirubin less than three times of the upper limit of normal. The workup to exclude other causes of liver injury is not documented, but this case fulfills the biochemical criteria for DILI.[19] The patient recovered fully.

One report linked autoimmune hepatitis in a patient with Hashimoto thyroiditis to isotretinoin after 3 months of therapy. Isotretinoin was stopped, steroids and azathioprine were initiated and the patient recovered.[20] The authors discuss isotretinoin, but fail to recognize the association of Hashimoto thyroiditis with autoimmune hepatitis.

In one series, 4 of 46 patients with Hashimoto thyroiditis had autoimmune hepatitis.[21] No further cases of isotretinoin associated autoimmune hepatitis were found.

A third patient developed mild derangement of liver enzymes on isotretinoin. After four months of therapy a biopsy found hepatosteatosis.[22] The patient had a low antitrypsin level, but no other underlying diseases that would explain the steatosis. The authors mention a similar case in the Roche database, though the workup of this patient is not reported. Assessing causation is difficult, since hepatosteatosis is frequently found on biopsy of asymptomatic patients with liver enzyme elevation. In one series of 149 patients with moderately elevated transaminases, but not on isotretinoin, 64% of biopsied patients had fatty liver.[23] No other cases reporting this association with isotretinoin were found, and a case series of 50 patients did not show changes associated with isotretinoin.[24]

Interpretation

Following approval of Isotretinoin in 1982, one case of probable DILI has been reported. Based on a single "possible" event, it is possible that isotretinoin may cause drug-induced liver injury (DILI), but not certain, and if it did it would appear to be extremely rare.[25] In the UK no death due to hepatobiliary disorders has ever been reported secondary to isotretinoin.[26] Isotretinoin certainly behaves differently to etretinate and acitretin and can be used in patients who have experienced liver injury due to these drugs.[25] Monitoring LFTs for drugs that cause DILI more commonly, like terbinafine,[15] is not useful,[13,15,27] and routine laboratory LFT monitoring for isotretinoin seems to be similarly unhelpful. Instead, informing the patient about the potential symptoms of DILI would be more appropriate. If symptoms of DILI (e.g. dark urine, abdominal pain,

generalized itch or jaundice) arise, LFTs need to be checked and isotretinoin withheld until workup has been concluded.

It should be noted that asymptomatic DILI, even if it crosses the threshold of laboratory diagnosis, may resolve on continuing therapy.[13,27] Adaptation is a transient increase in liver enzymes, but by definition does not progress to DILI and is not clinically relevant. This is what we commonly see in isotretinoin patients.[13,27,28] McElwee reports a patient with a baseline AST 41U/L which increased to 235U/L after 7 days of therapy only to normalize thereafter on continued therapy.[29] Given the available data, we believe that isotretinoin behaves similarly to other drugs like aspirin and heparin, that increase liver enzymes without causing DILI.[13]

The data presented does not suggest that baseline monitoring is helpful, particularly in younger healthy patients. Blood tests will likely find spurious elevations that may be irrelevant, but need further work up.[30,31] The level of abnormality is not necessarily a guide to clinical significance;[30,31] and is independent of the likelihood of isotretinoin-associated DILI. Given the age group it should be noted that activities like weightlifting lead to increases in liver enzymes for at least a week,[32] and that muscular diseases like limb-girdle muscular dystrophy may present only with elevation of liver enzymes as a reflection of muscle damage.[33]

LIPIDS

Current Recommendations:

BNF and EMC - Measure serum lipids before treatment, 1 month after starting and then every 3 months (reduce dose or discontinue if serum lipids persistently raised)[1,4] The BAD guidelines recommend additional fasting lipids at 4–6 weeks and then repeat tests every 3 months.[5]

Interpretation:

Lipid abnormalities were the subject of a review from 2016 that followed the format and methodology of a CAT.[8] Isotretinoin reliably increased triglyceride levels by 20-40% and reduced high density lipids. Due to the brevity of treatment this is unlikely to increase cardiovascular risk.[34] Hypertriglyceride-associated pancreatitis is an exceedingly rare adverse event with isotretinoin, which is now thought not to occur in patients with fasting triglycerides <2000mg/dL (22.6mmol/l)$^{-1}$.[35] The drug information for isotretinoin may be explained by the outdated lower triglyceride threshold for pancreatitis when the label was developed.[4,8] Triglyceride-induced pancreatitis has only been reported in three patients who were older than 35 years and had elevated triglycerides at baseline. The fourth patient was part of a glioblastoma trial and further information is not available. None of the patients were monitored. Idiosyncratic pancreatitis due to isotretinoin is a very rare but real adverse event.[36] It is poorly understood, but more frequent than hypertriglyceridemia associated pancreatitis. Patients need to be warned.[36]

Triglyceride-induced pancreatitis for younger patients is virtually nonexistent, (i.e. has never been reported) thus baseline triglyceride monitoring is unnecessary for typical teenagers if they have no other risk factors for elevated triglycerides.[37-39]

It is appropriate to check baseline triglycerides in those who have risk factors for elevated triglycerides based on truncal obesity, family and personal history, or signs of insulin resistance, like acanthosis nigricans.[40-42] These patients could have their fasting triglycerides checked after 4 weeks of therapy. If they are not significantly elevated, no further monitoring is warranted.

Monitoring of triglycerides after 2 months has no utility,[9,37,43,44] unless the isotretinoin dosage is changed. The exception is high-risk patients, where treatment interruption, dose reduction and diet intervention,[45] possibly even fibrates, may be necessary – these patients are rare exceptions and can be identified at the beginning of their therapy.[8]

FULL BLOOD COUNT (FBC)

Current Recommendations:

BNF + EMC - FBC monitoring not recommended.[1,4] The BAD guidelines recommend full blood count before treatment, at 4–6 weeks and then every 3 months.[5]

Evidence Found:

84 papers were identified, 25 were included for review (Diagram 2) and Table 1

This review includes 14 clinical studies with a total of 19,270 patients. Mild changes in FBCs were noted in several studies, and in the package insert,[4] however none reached clinically significant levels. Seven authors concluded that routine FBC monitoring was unlikely to be of clinical use, due to the rarity of significant abnormalities[37,44,46-50].

11 case reports were identified that discussed haematological abnormalities in patients taking oral isotretinoin. There were three cases of agranulocytopenia/neutropenia. In two cases isotretinoin was felt to be the probable trigger,[51,52] however in the third case the patient displayed an ongoing mild neutropenia for 30 weeks despite drug cessation, suggesting benign ethnic neutropenia, or cyclical neutropenia may be more likely.[53] Two cases of thrombocytopenia were noted in the literature. In one case the patient had also received cephalexin, however isotretinoin was felt more likely given the prolonged duration of the thrombocytopenia.[54] In the second case, rechallenge confirmed isotretinoin as a cause.[55]

Anaemia is often listed as a common side effect in the product information,[4] however about 10% of women in the US have iron deficient anaemia.[56] Iron deficiency anemia can be associated with nodular cystic acne and improve following treatment with isotretinoin.[57] One case of B12/folate deficient anaemia was identified during a course of isotretinoin, after the patient developed colitis.[58] However, given no prior FBC monitoring was performed it is difficult to be certain if a pre-existing deficiency was unmasked by isotretinoin, rather than driven by it.

Interpretation

Mild haematological abnormalities are common in patients on isotretinoin. However of 19,270 patients enrolled in a range of clinical studies in this review, no serious adverse drug reactions were noted on FBC monitoring.

Based on case reports, there are two probable cases of isotretinoin induced neutropenia, and two of thrombocytopenia. It is reassuring to note that isotretinoin was not identified in a multi-national study of drug-induced agranulocytosis and it is not considered a drug of high risk.[59] It is likely that the risk of agranulocytosis is lower than the 0.6 cases per 10^6 users/week that was found for doxycycline.[59] To evaluate such rare events, one would likely need a cohort study sized in the 100,000s or perhaps even millions for stable estimates. The question then is whether quantification is necessary for AEs which are rare and not amenable to prevention, or indeed early detection, such as thrombocytopenia, given the half life of thrombocytes is 7-10 days. Given this degree of rarity, routine monitoring is no longer recommended by either the BNF[1] or EMC[4] (although it is still referred to in the BAD guidelines from 2010[5]).

However, sepsis develops rapidly in the setting of agranulocytosis thus it may be prudent to warn patients of symptoms of blood dyscrasias (e.g. sore throat, fever, severe malaise) rather than to monitor blood at monthly intervals. For Dapsone, even weekly monitoring has been insufficient to prevent lethal agranulocytosis-induced sepsis, and dapsone, or even terbinafine, have more reports of agranulocytosis than isotretinoin has.[60] In addition no death due to hematological disorders has been reported in the UK.[26]

THYROID FUNCTION TESTS

Current Recommendations:

No monitoring recommended. Thyroid function abnormalities not listed as AE.[1,4,5]

Evidence Found:

45 papers were identified from our pubmed search, of which 10 were included for review, one was excluded as irrelevant based on the full text and two more were found based on references (Diagram 3 and Table 1).

Interpretation: Bexarotene is a related retinoid and highly specific for retinoid X receptors and well known to cause central hypothyroidism, but isotretinoin has not shown this affinity. Thyroid abnormalities secondary to isotretinoin have been reported since the 1980's,[61-66] but the number of cases is small, and no pattern of timeline or abnormalities has emerged to support causation. Since the 1980s prospective cohort studies have followed isotretinoin patients to investigate the influence of isotretinoin on hormonal homeostasis[49,66-70]. Some of these studies found mild changes of thyroid hormones, but none were clinically significant. National guidelines in the US[71] and the UK[72] do not recommend screening for thyroid disease in asymptomatic patients. Since 1983 19 cases of non further specified endocrine disorders have been reported in the UK, none lethal.[26] In summary, thyroid test screening in patients on isotretinoin is likely unnecessary in the asymptomatic.

MUSCULOSKELETAL

Current Recommendations:

No monitoring recommended. Myalgia, arthralgia and rhabdomyolysis are listed as side effects.[1,4] The BAD guidelines do not recommend monitoring but note that myalgia, arthralgia and increased serum creatine phosphokinase (CK) values have been reported in those undertaking vigorous physical activity, with risk of progression to potentially life threatening rhabdomyolysis.[5]

Evidence Found:

74 papers were identified from our pubmed search, of which 31 were included for review (Diagram 4 and Table 1).

Isotretinoin has been associated with a range of musculoskeletal side effects, including precipitation of acne fulminans, arthralgia, achilles tendonitis,[73] myalgia without CK elevation, and hyperCKaemia both with/without development of rhabdomyolysis[48,74-83]

Myalgia and mild transient elevations in CK are common, and were observed in 20% of patients in a small series[48]. Significant elevations are much less frequent, with Manfredini[74] detecting CK >5 x upper reference range in 1.2% of patients and Landau[82] noting CK>5000 in 1.6% of patients (though Laundau's was a military population). Multiple factors can influence CK including ethnicity, age, sex and physical activity[84]. The relevance of these elevations in CK remains disputed. Transient elevations of CK with exercise are common in young fit individuals, with Kenney noting levels as high as 35.056 IU/L in healthy training military recruits.[85] Without other aggravating factors such

as sepsis, dehydration or acidosis, the risk of AKI in rhabdomyolysis is much lower in patients with CK levels less than 15 to 20000 IU/L.[86] Indeed, clinical trials generally define statin myotoxicity as myalgia with CK elevation >10xupper reference limit[87]. Thus in young healthy patients, even relatively high CK levels (>5xupper reference range) are unlikely to precipitate rhabdomyolysis. It should also be noted that elevations in CK do not always correlate with symptoms of myalgia (of Landau's[82] 8 patients with a CK above 5000, only two were symptomatic). Conversely, severe myalgia with significant proximal weakness/stiffness has been reported with minimal change in CK levels,[79,88]though there may be a role for L-Carnitine for these symptoms[89]. Our literature review identified 8 cases of rhabdomyolysis secondary to isotretinoin,[75-77,80,81,83,90,91] with one fatality.[80] This has occurred with as little as 20mg daily dosing, though cases often note recent vigorous exercise as a potential trigger.

Interpretation:

Whilst the incidence of rhabdomyolysis is unknown, given the paucity of case reports, it is likely to be rare, but not totally so. In the UK about 500 cases of musculoskeletal disorders have been reported since 1983, that is about 12 per year, none of them lethal.[26] If these cases are rapidly precipitated by vigorous exercise, routine CK monitoring is likely ineffective. Education regarding limiting vigorous physical activity and identifying clinical symptoms of rhabdomyolysis (fatigue, myalgia and myoglobinuria) are a more effective strategy. For statin therapy, rhabdomyolysis is a significant problem. The lipid expert panel has developed algorithms for athletes that suggest therapy breaks, dose adjustment, or therapy changes based on CK results.[92]

These cannot be applied directly to isotretinoin, but the approach may be helpful in select cases.

Limitations

This review used published data of adverse events and thus will only identify a small subset of cases that have occurred; for the UK the estimate is that the yellow card system only identifies 10% of all serious adverse events.[93]

Isotretinoin has been on the market for nearly 40 years and based on usage data from 2013-2019 we estimate that isotretinoin has been prescribed in the US alone to at least 10.000.000 patients.[94] In the UK none of the organ systems discussed have been associated with death in the yellow card system, which confirms the literature as presented.[26]

The interest in it's adverse effects has been substantial since marketing began and consequently, the literature is very broad and has included reports of associations that are most likely coincidental, and over the 40 years have not been observed again. Whilst none of the cohort studies included were not powered to identify very rare adverse events, given the number of papers and cohort studies we are optimistic that the range of adverse events that we identified is representative. In addition we have limited the scope of this review purely to the question to routine laboratory monitoring, and whether the clinical characteristics of the reported adverse events meant that they can be detected and prevented with laboratory tests. Frequency of these events and pharmacoeconomic analysis can only be estimated with exact data, which we do not have.

Discussion and clinical message

Our review could not identify a single blood test that seems reasonable to perform routinely, given the rarity of the adverse outcomes identified in the literature in healthy young patients, or the rapidity of their clinical development. While more systematic research is always desirable, this would have to be population wide for large countries, or the EU, to accurately detect and quantify adverse events for isotretinoin, however, fourty years after market introduction the description of rare events that may change this recommendation is unlikely.

Rather than routine, we believe that blood tests need to be individualized based on risk factors. Patients with significant obesity, acanthosis nigricans, diabetes, or history of significant hypertriglyceridemia may benefit from baseline triglycerides, but the overwhelming majority will never reach the fasting 2000mg/dL-1 that put them at risk for pancreatitis.

Liver function tests will frequently be elevated on isotretinoin but the risk of DILI is negligible, if it even exists, and routine monitoring is not helpful. Minor cell death is part of liver adaptation to various drugs. The liver is resilient and has enormous repair capacity. It tolerates up to 70% resection[95] and living partial liver donors expect e.g. coagulation abnormalities to resolve in a week or two.[96]

Patients need to be informed about isotretinoin's rare adverse events, particularly pancreatitis and rhabdomyolysis, so they are aware to present should symptoms develop.

However, our findings suggest that routine monitoring may be falsely reassuring without improving safety. It likely drives over-investigation of spurious results, generating avoidable healthcare costs and causes confusion and anxiety until results are correctly evaluated. It should also be noted that the adverse events we identified in this review are considered so irrelevant that regulatory agencies have not found it necessary to react with package insert amendments, or black box warnings. We agree with that assessment.

Clinical scenario

We treated the patient with isotretinoin without laboratory monitoring. He was counselled on symptoms that should prompt laboratory evaluation, but remained well throughout the course with resolution of his acne and mild dry skin and cheilitis.

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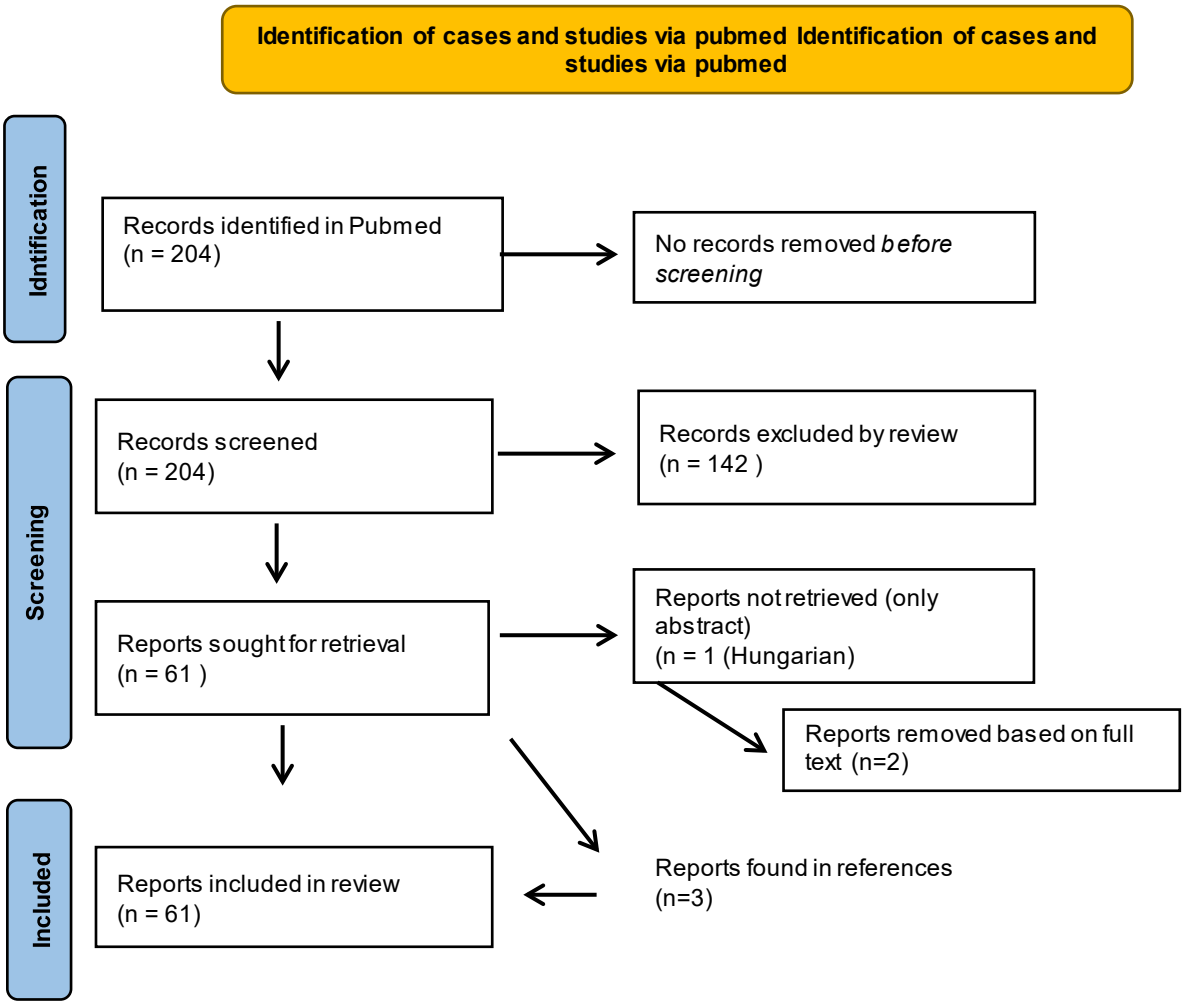
Study type	N – studies	N - patients
Liver		
Case reports	9	9
Cohort studies - prospective	8	1408
Cohort studies – unclear or retrospective	28	23358
RCTs	6	397
Review or meta-analysis	10	NA
Thyroid		
Case reports	6	6
Cohort studies - prospective	6	233
Hematology		
Case reports	10	10
Cohort studies – prospective	4	302
Cohort studies – unclear or retrospective	6	17074
Review or meta-analysis	1	17915
Muscle		
Case reports	14	15
Cohort studies - prospective	1	89
Cohort studies – unclear or retrospective	4	1076
Review or meta-analysis	3	NA

Table 1: Type of studies and number of patients

Diagram 1: Liver PRISMA – online material for all PRISMA Diagrams (online supplement)



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Diagram 2: Complete blood count PRISMA (online supplement)

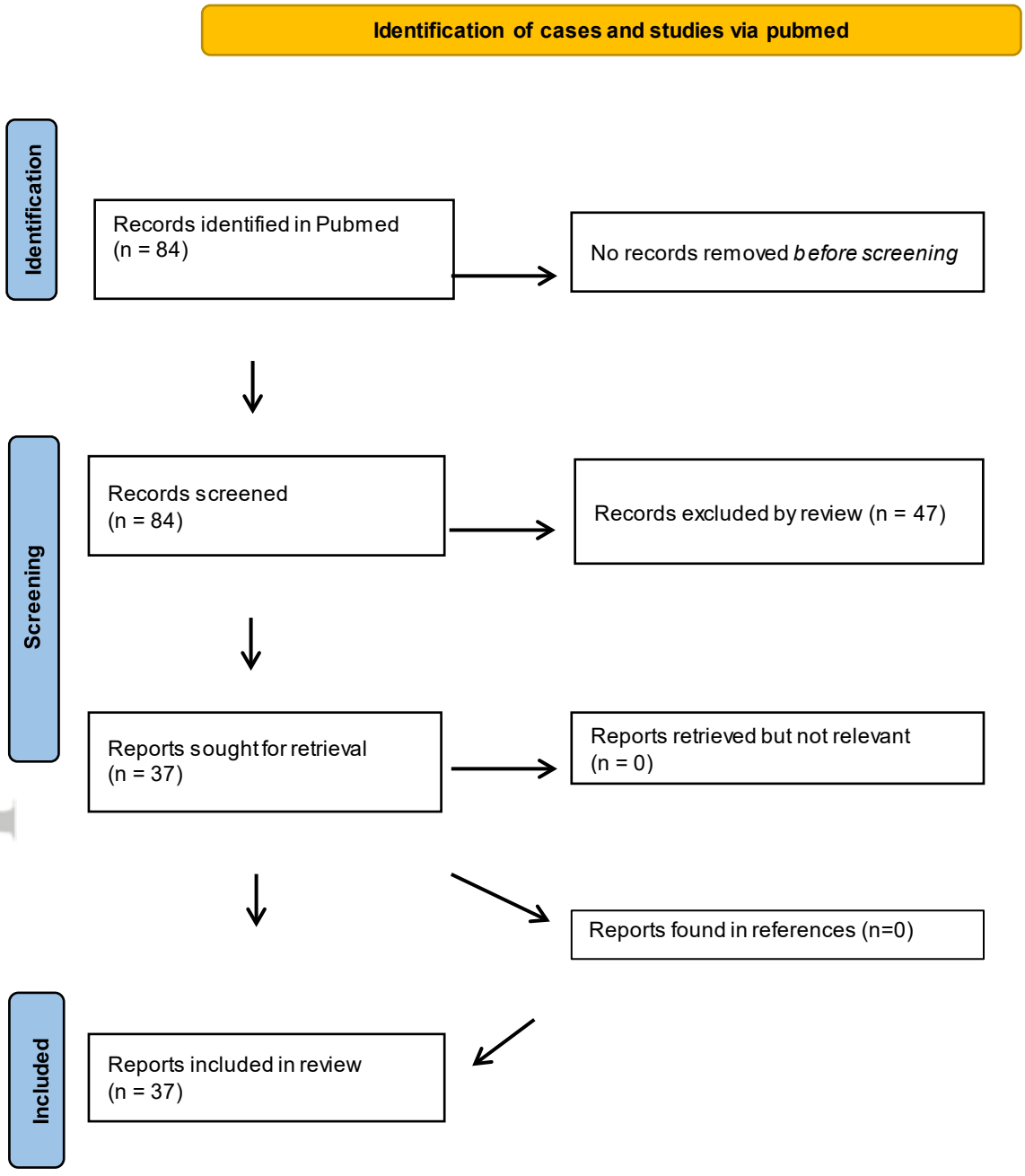


Diagram 3: Thyroid Function PRISMA (online supplement)

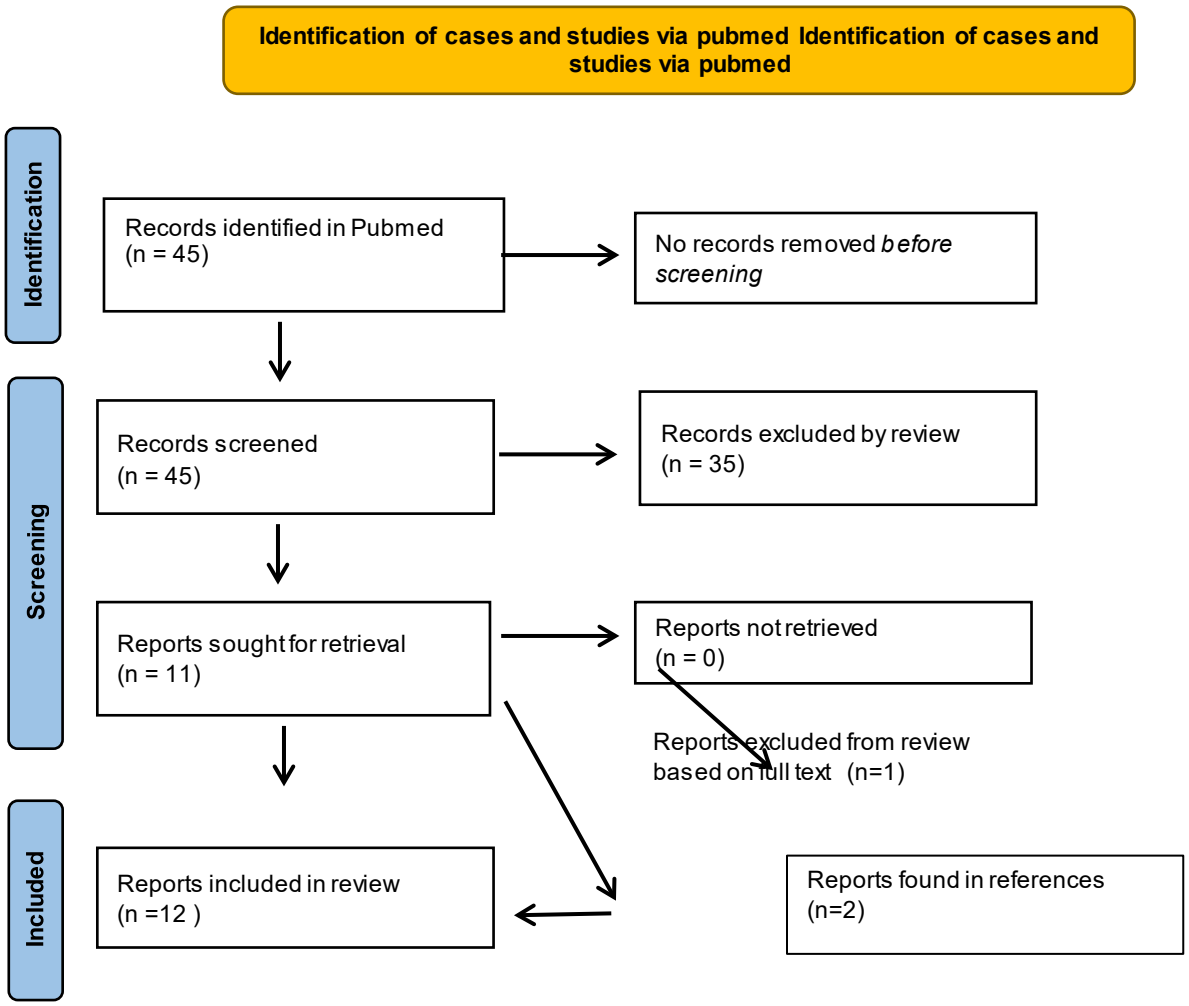
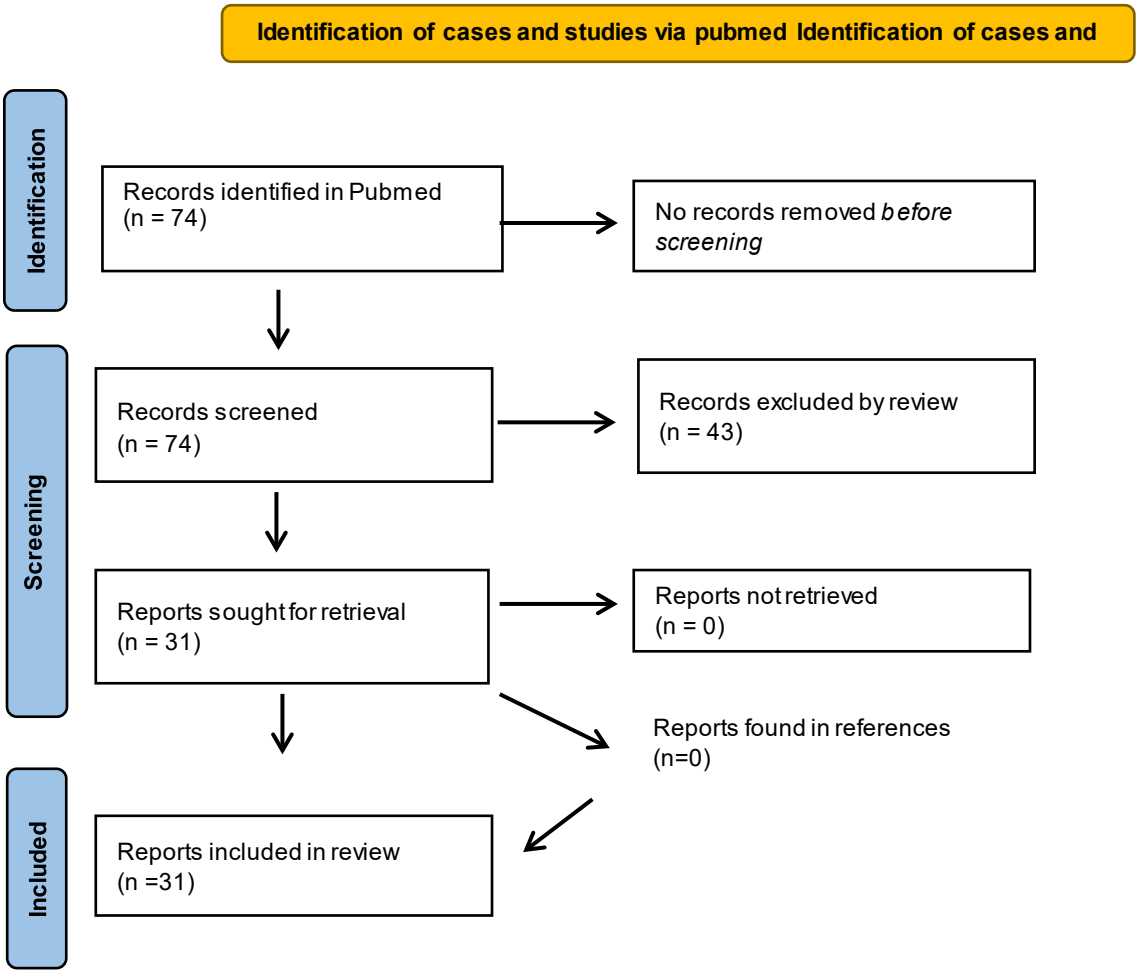


Diagram 4: Musculoskeletal PRISMA (online supplement)



Appendix 1: Search strings

Isotretinoin and Liver

("Isotretinoin"[Mesh] OR isotretinoin[tiab] OR accutane[tiab]) AND ("Liver"[Mesh] OR "Transaminases"[Mesh] OR liver*[tiab] OR transaminase*[tiab]) = 204 results

Isotretinoin and CBC

("Isotretinoin"[Mesh] OR isotretinoin[tiab] OR accutane[tiab]) AND ("Blood Cell Count"[Mesh] OR "Agranulocytosis"[Mesh] OR "Anemia"[Mesh] OR "Thrombocytosis"[Mesh] OR "complete blood count"[tiab] OR "complete blood counts"[tiab] OR "blood cell count"[tiab] OR "blood cell counts"[tiab] OR agranulocytos*[tiab] OR granulocytopenia*[tiab] OR anem*[tiab] OR thrombocythemi*[tiab] OR thrombocytos*[tiab]) = 84 results

Isotretinoin and Thyroid

("Isotretinoin"[Mesh] OR isotretinoin[tiab] OR accutane[tiab]) AND ("Thyroid Gland"[Mesh] OR thyroid*[tiab]) = 45 results

Isotretinoin and Rhabdomyolysis

("Isotretinoin"[Mesh] OR isotretinoin[tiab] OR accutane[tiab]) AND ("Rhabdomyolysis"[Mesh] OR "Muscles"[Mesh] OR rhabdomyolys*[tiab] OR muscle*[tiab] OR muscular[tiab]) = 74 results