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Metformin lactic acidosis: Should we still be afraid?

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ABSTRACT

Metformin, the first choice drug for type 2 diabetes treatment in all stages of therapy, and one of the most widely prescribed anti-hyperglycemic agents worldwide, represents a rare example of an old drug which continues to display new beneficial effects in various fields. However, lactic acidosis (LA) persists as a serious adverse effect. LA incidence is low and is not necessarily determined by the administration of metformin. Unfortunately, the concern for this complication has negatively affected the drug use, particularly in chronic kidney disease, which may impair drug excretion, and in congestive heart failure and chronic liver disease, which may promote lactate accumulation. This review describes how not only these historical contraindications have been considerably scaled back, though rather a recent large body of evidence supports a protective effect of biguanide on kidney, heart and liver and, maybe, against lactic acidosis itself.

It is worthy to slow down both contraindications and precautions to metformin use, not to deprive a significant number of diabetic patients, as those with kidney, heart and liver comorbidities, from its potential benefits, and not to hamper in the near future the putative advantages in a wide spectrum of conditions outside of diabetes.

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1. Introduction

Biguanide derivatives have been introduced in diabetes mellitus treatment in the 1950's. However, phenformin and buformin were withdrawn two decades later in almost all countries throughout the world due to frequent cases of life-threatening lactic acidosis (LA) [1]. Metformin, firstly introduced in Europe as "Glucophage" by Jean Stern in 1957, was registered in U.S. in 1995 [2]. A few years after its introduction into the American market, metformin has become the drug of choice in people with type 2 diabetes (T2DM), and it is still indicated as the preferred initial pharmacological agent, to be continued as long as tolerated and not contraindicated, both in monotherapy and in combination with other oral and subcutaneous antihyperglycemic drugs [3].

Over the years, metformin has been shown to exert a very wide range of positive pleiotropic effects in addition to its anti-hyperglycemic action. Meanwhile, the risk of LA associated with its administration progressively appeared less important than previously thought [4].

This narrative review mainly focuses on protective effects induced by metformin on kidney, heart and liver, whose impaired function is historically considered a contraindication to the drug use due to the risk of LA.

2. Lactic acidosis by metformin

The most common adverse events associated with chronic use of metformin are gastrointestinal complaints (e.g., diarrhea, nausea, metallic taste). Vomiting is less common, generally in the case of gastrointestinal diseases coexistence [5]. Long-term use of metformin may be associated with a biochemical deficiency of B12 vitamin, whose levels should be periodically measured, especially in patients with either anemia or peripheral neuropathy [6].

Unfortunately, metformin use has also been associated with a very rare, though more dangerous adverse event, lactic acidosis (LA).

2.1. *Incidence of LA in metformin users*

Association of metformin with LA is mainly based on historical data on phenformin, a biguanide exhibiting a well-defined hyperlactatemic effect which led to its withdrawal in most countries by the end of 1970s. The two drugs have different pharmacological characteristics, that could explain the much lower incidence of LA with metformin (0–0.09 case per 1000 patient-years) than phenformin (0.25–1 case per 1000 patient-years) [7].

Overall, LA by metformin appears as an extremely rare condition, with most estimates of <10 cases per 100,000 patient-years of exposure [8], even lower (5 cases per 100,000 patient-years), when considering subjects without renal disease [9]. In a study on 50048 T2DM patients from the UK General Practice Research Database [10], LA occurrence was very rare (6 cases total) and did not differ between those who received metformin vs. other oral anti-hyperglycemic agents. Likewise, a systematic review and *meta*-analysis of prospectic comparative trials and observational cohort studies covering 70,490 metformin person-year and 55,451 non-metformin person-year, did not found any evidence about an association between metformin and an increased LA risk (or increased lactate levels) compared to other anti-hyperglycemic agents [11]. In a systematic review by Inzucchi et al., LA overall incidence in metformin users varied across studies from approximately 3 per 100,000 person-year to 10 per 100,000 person-year, being generally indistinguishable from the background rate in the overall population with diabetes [12]. In line with these findings, a recently published case-control study, including 10652 T2DM patients followed for 4 years, registered an incidence rate of acute hospitalization with LA of 391/100,000 person-year but no increased risk with the use of metformin (adjusted OR 0.79; 95% C.I. 0.54–1.17) [13].

2.2. *Pathophysiology and diagnostic/nosological framework of LA by metformin*

Metformin primarily acts in the liver, where it suppresses the enhanced basal endogenous glucose production in T2DM patients by inhibiting gluconeogenesis. Despite metformin has been used for a long time, how the inhibition process works, partially remains still unclear. Over the years, several studies have supported multiple molecular mechanisms. The most important seems the inhibition of the mitochondrial respiratory chain in the liver, which leads to AMPK activation, enhancement of insulin sensitivity and cAMP lowering, with a reduced expression of gluconeogenic enzymes [14]. Studies on hepatocytes and animal models have demonstrated that the main target may be the non-competitive inhibition of the redox shuttle mitochondrial enzyme glycerophosphate dehydrogenase, leading to an altered hepatocellular redox state and, therefore, a decreased conversion of lactate and glycerol to glucose, resulting in a decreased hepatic gluconeogenesis [15]. According to these

mechanisms, metformin may enhance plasma lactate levels by inhibiting in the liver the clearance of lactate and, mostly, complex 1 of the mitochondrial respiratory chain, thus determining a reduced oxidation of pyruvate. As a consequence, NADH levels rise and oxidative phosphorylation decreases, with an inadequate recycle of the large quantity of H+ from ATP hydrolysis [8,16].

Therapeutic doses of metformin determine circulating drug levels generally not exceeding 2 μg/mL [17], and normal or slightly increased (usually less than 2 mmol/L) basal and postprandial lactate levels [18]. Other studies have consistently demonstrated no increase in serum lactate concentrations using metformin [19]. This is related to the very efficient hepatic lactate clearance (by conversion back to glucose thanks to the Cori cycle) reaching a rate of 320 mmol/h, which far exceeds that of normal lactate production [16].

When metformin is involved as LA cause, it abnormally accumulates in the bloodstream. This typically happens in the case of overdosing/intoxication or chronic/newly acquired renal failure (metformin circulates in the plasma unbound and is erased immodified mainly by kidneys). Concentrations >5 μg/mL are generally found [20], with the highest value ever reported of 432 g/L in a case of voluntary metformin intoxication [21].

On the other hand, LA appearance in a patient taking metformin may be favoured by impaired lactate clearance if liver failure coexists, or by lactate overproduction from hypoxic tissues in the case of respiratory and/or circulatory failure.

Therefore, to label a LA as metformin-induced, three key criteria must be met: high lactate concentration, low pH, and known plasma metformin concentration. Without these, particularly if circulating metformin level is missing, it is impossible to distinguish between LA by metformin accumulation in the setting of overdosing or kidney failure and LA by systemic conditions (sepsis, cardiac failure, haemorrhage, etc.) in a patient taking metformin in which biguanide use may be merely concomitant, without any causal role [22].

To better categorize LA causes, a diagnostic paradigm has been proposed by Krowl et al., according to which a causal link with metformin may be defined if lactate is >5 mmol/L, pH < 7.35 and metformin circulating level >5 mg/L [23]. Unfortunately, metformin assay is not readily available in emergency wards, thereby making this classification tool difficult to use in today's clinical practice. Moreover, therapeutic, as well as threshold concentrations for metformin accumulation, have never been defined, and are probably hard to consider as influenced by variations in the gene coding for metformin transporter proteins [24].

The acronym MALA ("metformin-associated lactic acidosis") first appeared in the literature in 1977, and was coined due to the difficulty to establish an either causal or merely coincidental role of metformin. It has been used to describe almost all cases of LA observed in a metformin-treated patient. Recently, its ambiguity has been strongly criticized by Lalau et al., since the sequence in which metformin therapy leads to drug accumulation, then hyperlactatemia, and finally LA is far from unavoidable [22]. The authors proposed a new paradigm, with distinct scenarios depending on the causal role of metformin accumulation and/or coexisting systemic diseases. A first condition was named LAMT ("lactic acidosis in metformin therapy"), when metformin concentrations are unknown. The most common situation is most likely MULA ("metformin unrelated lactic acidosis"), in which metformin concentrations are within the reference ranges, very low or moderate, and a concomitant systemic disease has the predominant causal role in hyperlactatemia. MILA ("metformin induced lactic acidosis") is instead characterized by isolated and massive accumulation of metformin, which plays a predominant causal role (as happens in voluntary metformin intoxication or acute kidney failure). Finally MALA, the intermediate condition between MULA and MILA, is the most complex case, with both metformin accumulation and one/more concomitant diseases responsible for hyperlactatemia. MALA probably accounts for a smaller proportion of cases.

2.3. *Outcome of LA by metformin*

The impact of LA by metformin on mortality is not clear, though it appears higher than 50%, as documented by several studies [25]. It has been reported that severity of neither metformin plasma concentrations nor arterial lactate levels or extent of metabolic acidosis may determine the likelihood of mortality. Rather, the most important prognostic factor seems the severity of an underlying condition which for example determines renal impairment from dehydration, vomiting or diarrhea, especially in elderly subjects having reduced glomerular filtration rate and/or continuing to take metformin [26,27]. A retrospective study involving 42 patients admitted to the intensive care unit concluded that LA related to intentional metformin overdose portends a much more favorable prognosis compared with LA by incidental metformin accumulation in the setting of a concurrent medical illness [28]. This finding is consistent with other publications reporting that patients with LA taking metformin often show better outcomes than those not, suggesting that in the presence of metformin even less severe comorbidities may be sufficient to determine LA [25]. The surprising results of a cohort study deserve to be mentioned [29]. In 44 metformin users and 118 nonusers admitted to emergency room with severe LA and sepsis, in-hospital mortality rate was significantly lower in those actively treated with metformin, despite their higher risk profile (older age, higher incidence of diabetes, cardiovascular diseases and acute kidney failure). Such results would delineate an even protective effect of metformin against LA most likely attributed to beneficial pleiotropic effects during critical illness. A recent review supports this interpretation reporting a series of potential ameliorative effects of metformin therapeutic doses in sepsis-induced organ failure, all mediated by AMPK activation, an energy sensing kinase with many downstream effects [30]. Among these, improved mitochondrial function, reduced oxidative stress, lower production of pro-inflammatory cytokines, less neutrophil accumulation/infiltration, and prevention of activation of transcription factors related to inflammation.

As a conclusion, it may be assumed that generally metformin at most limits patients' ability to cope with an increase in circulating lactate levels induced by an intercurrent event, which is the definite LA trigger. On the other hand, the true metformin/LA relationship in the clinical practice largely remains unproven, since incidence and mortality esti-

mates, as reported in the literature, may be confounded by multiple factors. First, data from trials or case-control studies, in which patients with LA risk factors are typically excluded and metformin is prescribed as indicated on the label, may have underestimated the real-life frequency of this adverse event. Second, the specific causal role of biguanide may be difficult to identify in the presence of potential confounding factors such as comorbidity, severe infection, dehydration or other clinical conditions favouring LA. This happens in several retrospective studies and case-series, which often do not provide sufficient details on the clinical setting (e.g., dose, duration and plasma concentrations of metformin, renal function over time, arterial lactate levels, and history of concurrent diseases) [26]. Data from a large pharmacovigilance database reported that three aforementioned criteria for LA diagnosis by metformin were met in just 10.4% of cases [31]. Finally, the variability of LA definition makes difficult to compare LA incidence across studies.

3. Revisiting hystorical metformin contraindications

Because of the negative experience with phenformin, ever since metformin has been approved for marketing, the FDA applies a boxed warning cautioning against drug use in the setting of conditions favouring LA: chronic or newly acquired renal failure, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors), age $\geq$65 years, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., unstable congestive heart failure (CHF)), excessive alcohol intake, severe dehydration, shock, sepsis, and hepatic impairment. In this context, it should not be forgotten that hyperglycemia alone may be a favoring factor for LA [32].

Even today, the left shadow of LA continues to float over metformin use, particularly in three clinical conditions frequently found in diabetic patients such as chronic kidney disease (CKD), which may result in impaired excretion of the drug, CHF and chronic liver disease (CLD) which can promote lactate accumulation [33].

3.1. *Chronic kidney disease*

Since circulating metformin is excreted unmodified in the urine, an area of longstanding debate is whether metformin can be safely used in CKD.

In the literature there are several clinical studies on diabetic patients suffering from different degrees of renal failure. A retrospective study reported a significant risk increase of either LA or elevated lactate concentrations in patients with mild to moderate renal insufficiency (<60 mL/min per 1.73 m^2) using a dose of recently prescribed metformin >2 g compared with patients under other therapies [34]. Instead, on a cohort of patients from the Swedish National Registry, the use of metformin in patients with eGFR 45 to 60 mL/min per 1.73 m^2 was associated with better outcomes than any other anti-hyperglycemic treatment, with a reduced risk of all-cause mortality, acidosis, and severe infection [35]. This risk was not increased even in metformin users with eGFR 30–45 mL/min/1.73/m^2. Likewise, Richy et al. observed no influence of metformin on LA incidence in patients with either normal, mild, moderate, or severe renal dysfunction [36]. Based on these data, and supported by a review including pharmacokinetic/metabolic studies, large case-series, retrospective studies, *meta*-analyses and a clinical trial, the FDA in April 2016 relaxed contraindications in impaired kidney function, expanding metformin use in patients with an eGFR till 30 mL/min/1.73 m^2. The revised guidelines state that metformin can be safely used in patients with stable, mild to moderate CKD, whilst remains absolutely contraindicated in patients with severe CKD (eGFR < 30 mL/min/1.73 m^2). Thanks to this, a large number of additional patients became eligible for drug use [37].

Over the years, novel clinical studies have continued to confirm metformin safety in CKD. A community-based cohort of 75,413 diabetic patients with time-dependent assessment of eGFR stage from January 2004 until January 2017 was studied for hospitalization for LA. Findings were replicated in 67,578 new metformin users and 14,439 new sulfonylureas users from 2010 to 2015. In these 2 real-world clinical settings, the need to use caution with metformin use was supported only in diabetic patients with a low eGFR of at least 30 mL/min/1.73 m^2 [38]. A recent publication of 3 complementary studies by Lalau et al. has added new evidence, indicating metformin treatment safe and still pharmacologically effective in moderate-to-severe CKD, when the dose is adjusted individually for the degree of renal failure [39].

The most interesting aspect on this topic is that not only the contraindication for metformin use in patients with CKD has been considerably scaled back, though rather a large body of evidence by preclinical and clinical studies in the last few years supports a renoprotective effect of biguanide. Metformin has been shown to exert positive effects both on *in vitro* and animal models representing different types of renal diseases, from acute kidney injury (AKI) to CKD [40–42]. In studies on humans, metformin has been shown to improve survival of patients suffering from AKI and CKD [43]. In an observational study on kidney transplant recipients linking Scientific Registry of Transplant Recipients data to national pharmacy claims data, Stephen et al. found that almost 10% of 51,523 recipients from 2001 to 2012 received metformin as part of their anti-hyperglycemic treatment regimen [44]. No data were provided on LA incidence, but metformin use resulted associated with improved allograft and patient survival. In an open-cohort study of 469688 T2DM patients, metformin significantly decreased the risk of severe kidney failure, including dialysis treatment, kidney transplant, and CKD stage 5, whereas sulfonylureas and insulin increased this risk [45]. Moreover, Bell et al. observed that current metformin use did not increase AKI incidence and was associated with a higher 28-day survival following incident AKI [46].

In a systematic review by Crowley et al. involving 17 observational studies, metformin exposure of patients with CKD, as well as CHF and CLD, was associated with a reduction of all-cause mortality [47]. In a recent publication, metformin has also shown a beneficial strong protective effect against CKD progression [48].

A number of potential underlying molecular mechanisms supports a direct renoprotective role of metformin. The drug, once entered the tubular cell mainly through the plasma membrane transporter OCT2, activates AMPK. This latter triggers pleiotropic downstream signaling pathways involved in

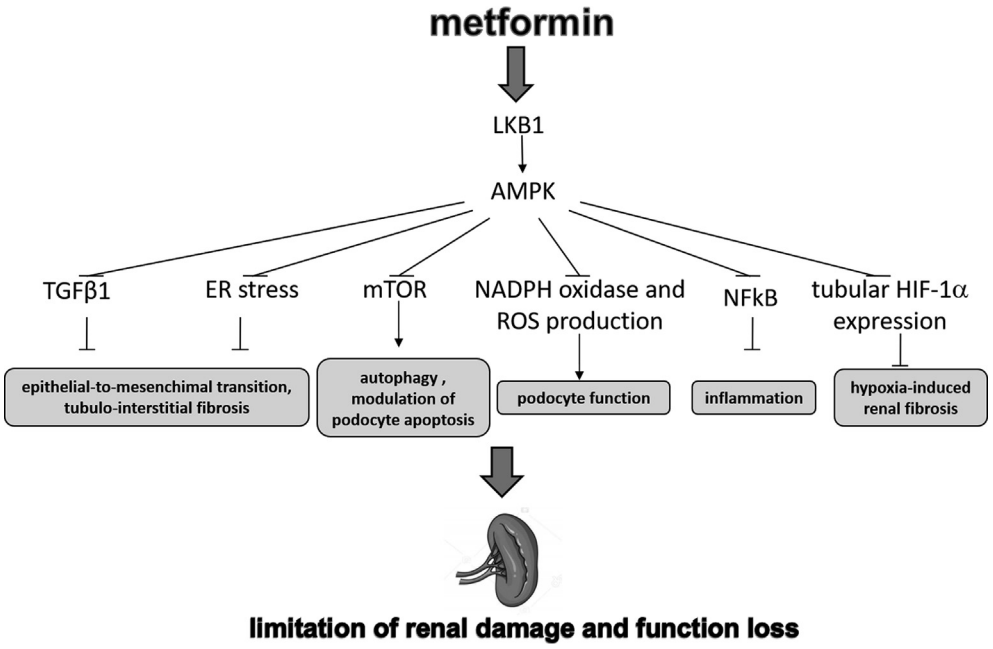

Fig. 1 – Direct renoprotective effects of metformin. AMPK, adenosine monophosphateactivated protein kinase; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; HIF-1, hypoxia-inducible factor-1; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; NFkB, nuclear factor-kappa B; ROS, reactive oxygen species; TGF-β1 transforming growth factor-β1.

various cellular processes which have been shown to protect the kidney against AKI and CKD (e.g., autophagy, inflammation, fibrosis, oxidative stress, and reactive oxygen species) [49] (Fig. 1).

Based on experimental evidence and some clinical observations, metformin seems to be a promising renoprotective compound. However, without the support of randomized clinical trials, it is premature to consider kidney disease as a therapeutic target for the drug. Actually, physicians must be aware that: (1) in T2DM patients using metformin, an extracellular volume contraction due to any reason may result in the development of AKI with LA even severe [50]; (2) since metformin excretion mainly takes place via the renal drug transporters OCT2 and MATEs [51], drug interaction upon these transporters may especially affect biguanide pharmacokinetics and plasma concentration; (3) due to the risks of a contrast nephropathy possibly resulting in LA, it is necessary to temporarily discontinue metformin, at least 48 h prior to any radiological examination involving intravenous iodinated contrast administration. About this, a recent study assessed metformin role in lactate production in a group of 162 diabetic patients with GFR > 60 mL/min/1.73 m^2 undergoing coronary angiography, indicating no risk of LA appearance at this degree of renal function [52].

3.2. *Congestive heart failure*

Patients with diabetes account for up one third of all CHF cases, with a risk almost twice higher for men and five times for women when compared with the general population [53]. For many years, there was reluctance to use the drug in patients with heart failure, due to tissue hypoxia, shift to anaerobic metabolism, and risk of LA. However, since observational studies and clinical experience suggested a minimal LA risk, similar to that of other antihyperglycemic drugs [54], both the US FDA (2006) and Health Canada (2010) have removed the absolute CHF contraindication from metformin, although keeping strong warnings.

In addition to metformin safety in the CHF population, a multitude of experimental studies and clinical observations have suggested a further benefit on mortality and morbidity reduction. A retrospective cohort study on 16,417 Medicare beneficiaries with diabetes hospitalized for CHF showed that patients discharged on metformin, compared with those discharged on either sulfonylureas or insulin, showed reduced mortality rate (13%) and readmission (8%) [54]. In a retrospective study on a large British database, metformin, both in monotherapy and in combination, was associated with a significantly reduced mortality rate compared with traditional treatment based only on diet and lifestyle changes in patients with newly diagnosed T2DM and CHF [55]. In particular, a decrease of mortality by 28% compared with a 45% reduction with ACE inhibitor/ARB and 24% with beta-blockers was found. In a systematic review on 34,000 patients with diabetes and CHF, metformin was associated with a 20% lower mortality, compared mostly with sulfonylureas [56]. In addition, interestingly, in a retrospective study on diabetic patients, metformin either in monotherapy or in combination, exerted a positive effect even on patients with advanced low ventricular ejection fraction (CHF in III and IV NYHA class), thus resulting in a potential reduction of all-cause mortality and composite endpoint (death or urgent heart transplant) risk, and an increase in left ventricular ejection fraction [57]. Also in the aforementioned *meta*-analysis by Crowley et al., metformin use resulted

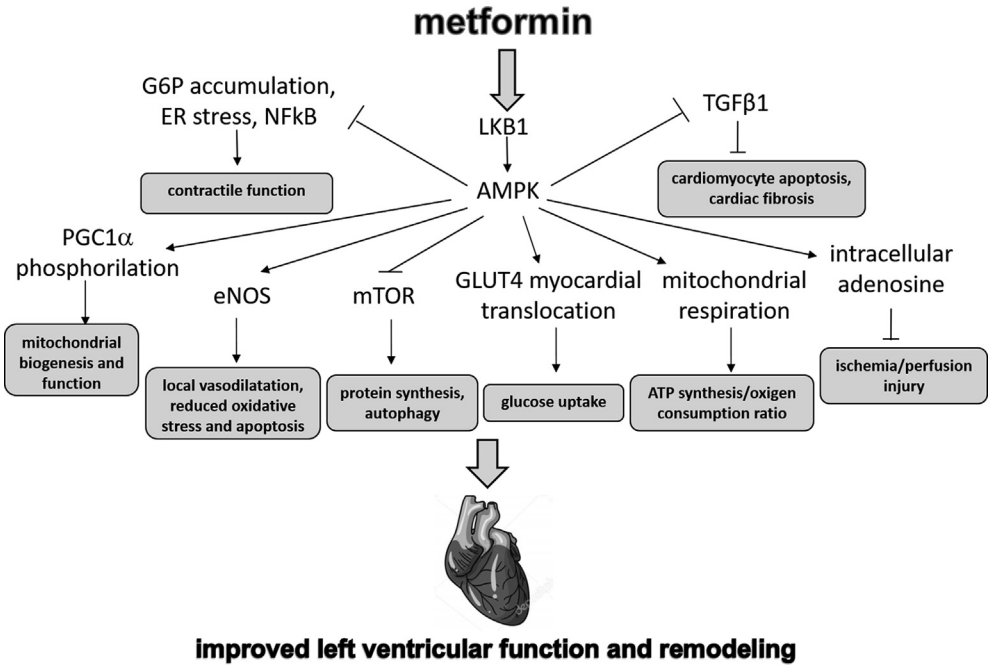

Fig. 2 – Direct cardioprotective effects of metformin. AMPK: adenosine monophosphateactivated protein kinase; eNOS: endothelial nitric oxide synthase; ER: endoplasmic reticulum; G6P: glucose 6-phosphate; GLUT4, glucose transporter type 4; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; NFkB, nuclear factors-kappa B; PGC-1α peroxisome proliferator-activated receptor gamma coactivator (PGC)-1; TGF-β1 transforming growth factor-β1.

associated with reduced all-cause mortality and fewer readmissions of diabetic patients with CHF [47].

Metformin, along with SGLT2 inhibitors, are actually suggested as the drugs of choice in patients with diabetes and CHF, being the only ones which can either prevent or improve this condition [58].

Mechanisms by which metformin exerts benefits on CHD are still not completely understood, but anyway they seem not related to the antihyperglycemic effect, since favourable responses have been found in models of heart failure without diabetes [59,60]. Metformin activates AMPK, a regulator of cardiac metabolism enhancing glucose uptake in insulin-resistant cardiomyocytes [61] and stimulating nitric oxide synthase in the myocardium, thereby preventing angiotensin II adverse effects. Moreover, the drug can stimulate autophagy, a process impaired in CHF [62], and exert a series of other effects (e.g., limiting interstitial fibrosis, reducing deposition of advanced glycation end-products, and inhibiting myocardial cell apoptosis), which can all hinder cardiac remodeling and hypertrophy (Fig. 2) [63].

Metformin may currently be considered safer than other antihyperglycemic drugs for CHF in diabetes cases, being increasingly suggested as the first-choice treatment [64]. Indeed, to clarify whether the drug actually improves risk and clinical course of CHF, more extensive and solid evidence from randomized clinical trials or observational studies is needed.

3.3. *Chronic liver disease*

Cirrhosis and diabetes are two clinical entities very often associated. It has been estimated that prevalence of T2DM in cirrhotic patients is five times higher than in those without cirrhosis [65]. Since liver plays a major role in gluconeogenesis, metformin prescribed to cirrhotic patients may cause LA by dramatically hampering lactate removal through this biochemical pathway. Therefore, CLD has always been considered, and still remains, a contraindication to metformin use, even though specific studies are lacking and published case reports are often restricted to subjects actively drinking alcohol, who do not represent the general population with cirrhosis and diabetes. Some clinicians are cautious to prescribe metformin even in patients with non-cirrhotic liver disease, believing that the drug might cause or worsen liver injury. This is not the case at all. Indeed, the literature is rich in data indicating favorable effects of biguanide in liver diseases.

Non-alcoholic fatty liver disease (NAFLD), a spectrum of conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and liver cirrhosis, is the most common CLD cause in Western countries, with a prevalence of 20–30% in the general population, till the 55% in T2DM patients [66]. Several animal and human studies outline the beneficial impact of metformin in this liver disease [67,68]. It has been demonstrated that metformin prevents and reverses steatosis and inflammation in a non-diabetic mouse model of NASH [67] and improves liver histology and alanine aminotransferase (ALT) levels in patients with NAFLD/NASH [68]. However, despite these results and the numerous potential beneficial effects (Fig. 3) [69], metformin is not indicated as a specific treatment for NAFLD/NASH by practical guidelines [70], as clinical evidence is not yet strong enough and two extensive *meta*-analyses concluded that the drug is not able to improve liver histology [71,72].

Interestingly, a large clinic/hospital-based cohort retrospective study assessed outcomes and safety of metformin

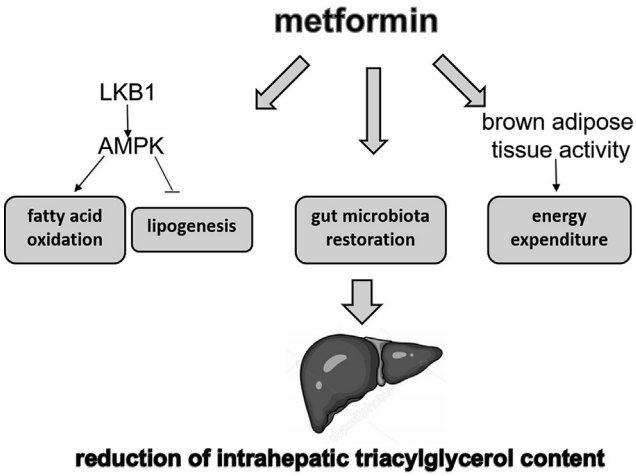

Fig. 3 – Potential beneficial effects of metformin in the treatment of NAFLD. AMPK, adenosine monophosphateactivated protein kinase; LKB1, liver kinase B1.

continuation in diabetic patients with various causes of cirrhosis and a wide range of severity degrees of liver impairment [73]. The study demonstrated an improved survival and a reduced risk of death by 57%, independent from liver impairment severity, as defined by Child-Pugh classification, only in the NASH-related cirrhosis. To notice, no patients developed LA or other serious complications.

Hepatic steatosis represents a key risk factor in the development of hepatocellular carcinoma (HCC). Studies on mice have found that early treatment with metformin to suppress liver-fat accumulation prior to the onset of NAFLD may help to prevent liver tumorigenesis induced by high-fat diet [74]. Several clinical data support advantages by metformin use on HCC risk and mortality in cirrhotic patients. A *meta*-analysis of 19 studies involving over five hundred thousand diabetic subjects suggested that metformin use reduced the ratio of liver cancer by 48% (OR = 0.52; 95% CI, 0.40–0.68) compared with nonusers [75].

More randomized clinical trials are still needed to confirm a role of metformin in improving survival of diabetic patients with CLD. To date, the drug may be considered safe and feasibly beneficial in preventing HCC, except for patients with Child-Pugh class C cirrhosis, for which greater caution is required.

3.4. *Atherothrombosis*

Diabetes, as known, is often complicated by cardiovascular conditions. In this context, the pharmacological treatment has been for long time object of debate. Though from the UKPDS Study emerged some potential benefits of metformin use in primary prevention of cardiovascular complications [76], this is often not considered in patients with cardiovascular conditions, as several matters have been arised on its safety, particularly for lactic acidosis complications.

Roussel R et al. studied 19,691 patients with diabetes from the international Reduction of Atherothrombosis for Continued Health (REACH) Registry, in order to evaluate whether metformin use was associated with a difference in mortality after adjusting for specific baseline variables and the propensity to receive metformin among patients with established CAD, cerebrovascular disease, or peripheral arterial disease [77].

The authors discovered mortality rates of the 6.3% (95% C.I.: 5.2%–7.4%) with metformin and 9.8% (95% C.I.: 8.4%–11.2%) without. Moreover, an association with lower mortality was mostly remarkable among patients with a history of congestive heart failure. The authors concluded that metformin use may decrease mortality among patients with diabetes when used in secondary prevention, also among those patients in whom its use is not now recommended. However, still prospective studies need to confirm its effect on survival in this specific subpopulation [77].

4. Final considerations

Currently, metformin is at same time one of the oldest and most widely prescribed anti-hyperglycemic agent worldwide, classified as an essential drug on the WHO list. Its use has settled down so strongly in the diabetic field that every development program for new antihyperglycemic agents routinely tests its investigational agent in combination with metformin. Hence, metformin is the most common therapeutic agent among fixed-dose combination drugs currently available in association with all marketed oral antihyperglycemics (sulfonylureas, glinides, thiazolidinediones, DPP-4 inhibitors, and SGLT2 inhibitors).

The extension of drug use has been achieved over the years despite the brake of historical contraindications generated by the negative experience with phenformin-associated LA. It cannot be excluded that stringent contraindications in prescribing practices may have contributed to metformin success as the first-line diabetes therapy. On the other hand, an excessive caution may have produced a detrimental suboptimal use of the drug and deprived a substantial number of patients as those with kidney, heart and liver comorbidities, from its potential benefit [33]. It has been estimated that only 65% of newly diagnosed T2DM patients are initially treated with metformin [78], which could lead to the alternative prescription of potentially more dangerous drugs (e.g., sulfonylureas, notoriously at high risk of severe hyoglycaemia in patients with renal impairment). Moreover, 85% of providers do not prescribe metformin in the presence of either a precaution or a contraindication [79], though an increase in LA incidence is not necessarily determined by its prescription [80].

Fear for LA development may slacken in the near future the putative advantages of using metformin in a large expanding spectrum of conditions outside of diabetes.

LA incidence in the setting of metformin therapy is objectively low, and the drug is not necessarily responsible of a LA event occuring in a patient taking this medication. Rather, the drug may play a contributory role as almost all reported cases present with independent risk factors for LA. Moreover, data from the literature unanimously underline the uncommonness of LA even in populations with comorbid moderate CKD, CHF, or CLD with impaired hepatic function, instead its benefits could exceed the potential dangers. Hence, a care-

ful enhancement of metformin use should be encouraged in these clinical conditions, provided that the therapeutic option is tailored to the potential risks and benefits of the single diabetic patient.

Waiting for further clarifications on this topic, some key points may be stressed. A strong warning towards the use of metformin should be strictly applied to patients with CKD 5, unstable CHF (particularly when accompanied by hypoperfusion and hypoxemia) and decompensated cirrhosis, due to their very fragile clinical situation.

To ensure safety in diabetic patients both with and without contraindications to metformin use, it is critical for healthcare providers: (1) to educate patients to temporarily discontinue the drug during acute intercurrent illness and situations causing kidney function impairment or extracellular volume depletion (for instance in case of gastrointestinal disturbances; (2) to warn patients against an excessive alcohol intake which could affect metformin effect on lactate metabolism and (3) to regularly monitor kidney function, especially in elderly subjects with a greater likelihood of suffering from hepatic and cardiac impairment, in order to implement an appropriate metformin dosage adjustment. In this view, the FDA 2016 guidelines recommend not to start the medication if the eGFR is <45 mL/min/1.73 m^2 and to discontinue the medication with an eGFR < 30 mL/min/1.73 m^2. In addition, patients with an eGFR between 30 and 45 mL/min/1.73 m^2 can continue to take the medication at a daily dose of 500 mg/bid, previous assessing the benefits and risks of continued treatment. Robust evidence has been recently provided by Lalau et al. [39] for rational dose adjustments in patients with an eGFR between 30 and 60 mL/min/1.73 m^2. Particularly, the authors selected a chronic dosage regimen of 1500 mg/day for patients with CKD stage 3a and 1000 mg/day for patients with CKD stage 3b. Furthermore, they suggested that low dose metformin (500 mg once daily) may be safe in patients with an eGFR between 15 and 30 mL/min/1.73 m^2.

In conclusion, metformin represents a rare example of an eternally young drug, with a fascinating veil of mystery on its mechanism of action and growing beneficial effects in various fields. To increase the number of people who can benefit from it, less contraindications and precautions for use are desirable.

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