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Review Article

The effect of N-acetylcysteine on metabolic dysfunction associated with fatty liver disease and polycystic ovary syndrome as metabolic disorders

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ABSTRACT

Metabolic dysfunction associated with fatty liver disease (MAFLD) and polycystic ovary syndrome (PCOS) are common disorders often related to metabolic syndrome. Insulin resistance, obesity, and oxidative stress contribute to the pathogenesis of both MAFLD and PCOS.

N-acetyl cysteine (NAC) is an antioxidant with anti-inflammatory, antiapoptotic, and insulin-sensitizing properties, and arises as a possible therapeutic option for MAFLD and PCOS. This review aims to investigate the effect of NAC alone or in combination on the metabolic parameters associated with MAFLD and PCOS. Using pre-defined keywords, PubMed, Google Scholar, and clinical trial.gov were systemically searched to identify related studies. A total of 10 studies related to MAFLD and 17 other studies related to PCOS were included. In conclusion, most of the included studies showed a promising impact of NAC in reducing elevated transaminases and the degree of liver steatosis in MAFLD through reducing oxidative stress and insulin resistance. Regarding PCOS, NAC was reported to have a positive effect on endometrial thickness, ovulation rate, and pregnancy rate either alone or when combined with clomiphene citrate. Further clinical trials are needed to confirm these results.

Keywords: *N-acetyl cysteine; metabolic syndrome; non-alcoholic fatty liver; metabolic dysfunction associated with fatty liver; polycystic ovary syndrome.*

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1. Introduction

1.1. Definition of metabolic syndrome

Metabolic syndrome (Mets) is a group of frequently co-occurring metabolic factors associated with cardiovascular diseases, type II diabetes mellitus (T2DM), and other metabolic disorders. The risk factors include elevated fasting glucose, central obesity, dyslipidemia, and elevated blood pressure **[1]**.

According to the 2009 harmonized definition from the International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), metabolic syndrome can be diagnosed by the presence of 3 or more of the following criteria **[1]**.

Central obesity, measured by waist circumference with ethnic consideration in Caucasian individuals, is approximately ≥ 94 cm in males and ≥ 80 cm in females.

Elevated fasting plasma glucose: (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed T2DM.

Elevated blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or medication for previously diagnosed hypertension.

Elevated Triglyceride level: ≥ 150 mg/dL (1.7 mmol/L) or lipid-lowering medication.

Reduced HDL cholesterol level: < 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or lipid-lowering medication. Both insulin resistance (IR) and central obesity are considered the main contributing factors for Mets and many metabolic disorders, such as metabolic dysfunction-associated fatty liver disease (MAFLD) and polycystic ovary syndrome (PCOS) **[2, 3]**.

1.2. MAFLD's definition, prevalence, and pathophysiology

MAFLD was formerly known as non-alcoholic fatty liver disease (NAFLD). The main difference between the two terms is that NAFLD was used to describe the presence of hepatic steatosis ≥ 5% without significant alcohol consumption and with the exclusion of secondary causes of liver disease, while MAFLD uses the same standard of liver steatosis combined with at least one of three criteria, including T2DM, overweight\ obesity, and cardiometabolic risk factors **[4, 5]**.

The spectrum of disease ranges from NAFLD, characterized by macrovesicular hepatic steatosis to hepatic inflammation ballooning with or without fibrosis referred to as non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma (HCC) **[6]**.

MAFLD is considered the main cause of HCC and liver transplantation worldwide. Although there is insufficient evidence on the prevalence of MAFLD in Egypt, current statistics suggest that more than one-third of the Egyptian population has had MAFLD, compared to a worldwide prevalence of about 25% **[7-9]**.

Based on the available data, Egypt has had one of the greatest incidence rates of MAFLD-related HCC in the world, rising by 89.8% between 1990 and 2017 **[10].** According to another study conducted in Egypt, the annual proportions of HCC due to MAFLD grew from 4.3% in 2010 to 20.6% in 2020, while the proportions associated with HCV decreased from 94.8% to 76.7% **[11]**.

Both insulin resistance (IR) and oxidative stress play a pivotal role in MAFLD pathogenesis. In the IR case, there is a reduction in the insulin antilipolytic effect, leading to significant production and deposition of free fatty acids (FFAs) in the liver. On the other hand, IR promotes de novo lipogenesis (DNL) in hepatocytes by activation of sterol regulatory element-binding protein 1c (SREBP-1c) **[12]**.

The increase of FFAs' production in the hepatocytes causes fatty acid oxidation system damage and mitochondrial dysfunction, resulting in the production of a large amount of reactive oxygen species (ROS), which in turn oxidizes fatty deposits to produce lipid peroxides and mediates an inflammatory response. ROS and lipid peroxides impair the hepatocyte's respiratory chain, causing oxidative damage to the mitochondrial genome, which generates a vicious cycle of oxidative stress by producing more ROS **[2]**.

Being related to metabolic syndrome, IR, oxidative stress, and obesity, the main approach in the management of MAFLD is lifestyle modification (weight loss and physical activity). Exercise has cardiometabolic and hepatic benefits and should be customized according to the patient’s preferences and physical abilities. In

MAFLD patients, weight loss of 3% to 5% has a beneficial impact on steatosis, but greater weight loss of more than 10% is required to improve NASH and fibrosis **[6]**.

Since there is still no definite cure and pharmacological agents focus on coexisting metabolic disorders like T2DM, dyslipidemia, and obesity. Vitamin E, semaglutide, and pioglitazone can be considered in certain NAFLD conditions **[6]**.

1.3. PCOS' definition, prevalence, and pathophysiology

Polycystic ovary syndrome (PCOS) is the most prevalent metabolic, endocrine, and reproductive disorder in women of childbearing age. PCOS combines various signs and symptoms and none of them is solely sufficient for its diagnosis **[13]**. According to the Rotterdam Consensus 2003, PCOS is diagnosed by two out of three features of oligo ovulation or anovulation, clinical or biochemical signs or symptoms of hyperandrogenism, and having a polycystic ovaries pattern on ultrasound, with the exclusion of other hyperandrogenic conditions such as congenital adrenal hyperplasia, hyperprolactinemia, Cushing syndrome, thyroid disease, and androgen-producing tumors **[14]**. **Table 1** shows the differences between organizations in the diagnostic criteria for PCOS. The estimated prevalence of PCOS varies from 6% to 10% in children and adults using the diagnostic criteria of the National Institutes of Health and Rotterdam or Androgen Excess and PCOS, respectively **[15]**.

Table 1. Different diagnostic criteria for PCOS in adult females before menopause [16]

Rotterdam	NIH	AE-PCOS
Includes 2 of the following: -clinical[a] and/or biochemical[b] hyperandrogenism. - oligo-ovulation or anovulation. -polycystic ovarian morphology [c].	Includes all the following: -clinical[a] and/or biochemical[b] hyperandrogenism. - oligo-ovulation or anovulation.	Includes clinical [a] and/or biochemical[b] hyperandrogenism and 1 of the following: - oligo-ovulation or anovulation. -polycystic ovarian morphology[c].

AE-PCOS; Androgen Excess and Polycystic ovary syndrome; NIH; National Institutes of Health.

[a]clinical hyperandrogenism can include hirsutism, female pattern hair loss, and/or acne.

[b]biochemical hyperandrogenism means excessive production and/or secretion of androgen.

[C]polycystic ovarian morphology is defined by ultrasound.

Although hyperandrogenism is known as the main cause of PCOS, the exact etiology has not been fully understood. Evidence proposed the role of many external and internal factors, including IR, hyperandrogenism (HA), genetic, epigenetics, and environmental factors, in the pathogenesis of PCOS. In addition, PCOS increases the risk of T2DM, cardiovascular disease, metabolic syndrome, anxiety, and depression **[17, 18]**. Progressive evidence shows that PCOS and NAFLD are linked; the pathophysiology of NAFLD in females with PSCOS is associated with IR, dyslipidemia, obesity, and HA. A case-control study found that hyperandrogenic PCOS females were at higher risk for developing NAFLD compared with PCOS females with no HA and healthy females, independently of BMI and IR **[19]**.

In PCOS women, IR is tissue-selective, while adrenal glands and ovaries remain sensitive to

insulin, liver, skeletal muscles, and adipose tissue lose their sensitivity **[20, 21]**. CYP17A1, the crucial enzyme in androstenedione and testosterone production, is enhanced by IR. On the other hand, hyperinsulinemia increases the blood level of free testosterone by the reduction of hepatic sex hormone-binding globulin (SHBG) **[22]**. In addition, hyperinsulinemia increases the thecal cells production of androgen by suppressing the production of insulin-like growth factor-1 (IGF-1) binding proteins. Moreover, the upregulation of IGF-1 inhibits folliculogenesis and accelerates the apoptosis of granulosa cells **[3]**.

Different studies found high levels of oxidative stress markers in PCOS patients. Elevated levels of ROS activate the nuclear factor-kappa B (NF-κB). NF-κB activates the production of pro-inflammatory cytokines like TNF-α and IL-6 that interfere with the insulin signaling pathway. Thus, oxidative stress leads to IR **[23]**.

In PCOS, therapy is tailored based on the clinical presentation and the patient's goals (trying to conceive, controlling irregular menstruation, losing weight, or getting rid of hyperandrogenic symptoms including hirsutism, acne, or androgenic alopecia) **[3]**.

1.4. N-acetylcysteine repurposing

Drug repurposing, or drug repositioning, is a technique of using an existing medication for a new indication or medical condition rather than one it has been approved for. Using a drug with established safety and efficacy has skipped the drug development process, and thus saved time and reduced the cost **[24]**.

N-acetylcysteine (NAC), the acetylated form of amino acid l-cysteine, is a precursor of thiol (SH) groups that stimulate glutathione production, thus scavenging free radicals. NAC is well known for its antioxidant and anti-inflammatory properties. Vastly used as an antidote in acetaminophen overdose hepatoxicity. Also, different effects of NAC on variable disorders such as contrast-induced nephropathy, non-acetaminophen drug-induced liver failure, chronic obstructive pulmonary disease, and pulmonary fibrosis have been proposed in clinical studies **[25]**.

2. Material and methods

This review aims to investigate the literature regarding the impact of NAC on oxidative stress, IR, and metabolic parameters compared with standard therapy in patients with MAFLD and PCOS.

2.1. Data sources and search strategy

A systematic and comprehensive search of major electronic databases such as PubMed, Google Scholar, and clinicaltrial.gov was done from the 1st of September to the 20th of October of 2024. Keywords and Medical Subject Heading (MeSH) terms such as “N-acetyl cysteine and fatty liver disease”, “N-acetyl cysteine and metabolic dysfunction- associated fatty liver disease”, “NAC and fatty liver disease”, “NAC and NAFLD”, “NAC and metabolic dysfunction-associated fatty liver disease”, “NAC and MAFLD”, “ N-acetyl cysteine and polycystic ovary syndrome”, “N-acetyl cysteine and PCOS”, “NAC and polycystic ovary syndrome” and “NAC and PCOS” were used to encompass consistent synonyms of each term. The present systematic search was limited to the English language.

2.2. Study screening and selection

Original English-written full-text clinical trials were assigned for inclusion in this review. Basic information on pilot studies, randomized control trials (RCT), and non-randomized trials was reviewed.

2.3. Eligibility criteria

Our inclusion criteria mainly focused on the published literature that concerned the effect of NAC in the management of both NAFLD and PCOS. Thus, RCTs, non-randomized controlled trials, and pilot studies available in full-text versions were included in this review. Abstract-only clinical trials and animal studies were excluded.

3. Results

A total of 78 and 55 studies of NAFLD/MAFLD and PCOS were found, respectively, during the scholarly search. After the elimination of duplicates, systematic review, meta-analysis, pre-clinical in vivo and in vitro, retracted, and non-related studies. The remaining qualified studies were 10 and 17 studies that evaluated the effect of NAC on NAFLD and PCOS, respectively. The consort flow chart of study selection is presented in **Fig. 1**.

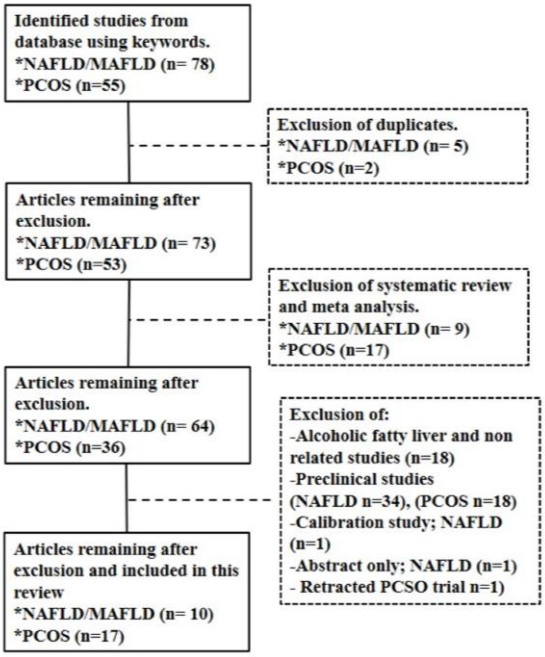

Fig. 1. Search strategy flowchart

3.1. Overview of included studies

According to study design and population, an overview of the included studies in our review is shown in **Tables 2 & 3**.

Table 2. Summary of included clinical trials reporting the effect of NAC on NAFLD as a condition of metabolic syndrome

Trial	Study design	Patient population	Intervention	Comparison	Outcome	Conclusion
Pamuk GE et al (2003) **[26]**	Uncontrolled trial For 1 month	Biopsy-proven NASH with elevated ALT and AST, Adult (n= 35)	NAC (600 mg/day) orally (n= 18)	control group (n= 17) was followed up without therapy	The therapeutic effect of NAC in the treatment of NASH	- A remarkable reduction in serum levels of AST and GGT only in the NAC group.

C. P. M. S. de Oliveira et al (2008) **[27]**	Prospective pilot for 1 year	Biopsy-proven NASH, adult patients (n=20)	NAC (1.2 g/day) plus metformin "MTF" (850–1000 mg/day), orally	----------	The efficacy of the combination of NAC with MTF on amino-transferases, steatosis, ballooning, and fibrosis.	- A significant improvement in steatosis and fibrosis. - A reduction of serum ALT, glucose, insulin concentrations, and the HOMA–IR index.
Khoshbaten et al (2010) **[28]**	RCT for 3 months	NAFLD, adult patients (n= 30)	NAC (600 mg twice, orally)	Vitamin C (1g twice, orally)	The effect of NAC on elevated liver enzymes and degree of steatosis.	- A reduction in ALT level and the size of the spleen with no significance on the degree of steatosis.
Claudia P. OLIVEIRA et al (2019) **[29]**	Open-label multicenter RCT for 12 months	Biopsy-proven NASH, adult patients (n= 53) 3 groups in proportion 2:1:1	Group 1: NAC (1.2 g/day) plus UDCA (15 mg/kg/day) plus MTF (850-1000 mg/day) Orally (n= 26)	Group 2: UDCA (20 mg/kg/day) plus MTF (850-1000 mg/day) Orally (n= 13) Group 3: NAC (1.2 g/day) plus MTF (850-1000 mg/day) orally (n= 14)	The impact of the combination of NAC plus UDCA, on the histological improvement of liver biopsy.	- The intergroup analysis revealed no differences among the 3 groups. - Intention-to-treat intragroup analysis of the NAC + MTF group showed an improvement in serum ALT level, steatosis degree, ballooning, and the NAFLD Activity Score (NAS)
Garicano Vilar E et al (2023) **[30]**	Randomized pilot study For 3 months	Adult patient with metabolic syndrome, at risk of MAFLD (FIB-4 < 1.3) (n= 27)	MetioNac® (S-adenosyl-L-methionine (200 mg), NAC (100 mg), thioctic acid (75 mg), and vitamin B6 (0.65 mg). 3 capsules per day, 2 in the morning and 1 in the evening plus MD. (n= 13)	The control group was on a semi-personalized Mediterranean diet (MD). (n= 14)	-The impact of METIONAC® on body weight and lipid profile. - The effect on serum ALT, AST, GGT, and glucose.	-The combinations of elements with different targets like METIONAC® may reduce the risk of MAFLD by improving Mets.
P. Babu Balagopal et al (2024) **[31]**	Double-blinded phase II, pilot For 4 months	Biopsy-proven MASLD- obese children with NAS score> 2 (n= 13)	Group1: NAC (600 mg/day) orally (n= 5) Group 2: NAC (1200 mg/day) orally (n= 4)	Group 3: Placebo, twice daily (n= 4)	The therapeutic effect of NAC on biomarkers of oxidative stress, inflammation and (IR), liver enzymes, liver fat fraction (LFF), and liver stiffness (LS).	- Both NAC groups resulted in similar results and were merged for final analysis. -NAC improved inflammatory markers (IL-6 and hs-CRP), oxidative stress markers (GSH), and IR (HOMA-IR). - Liver enzyme reduction. -Improvement of LFF and LS. - No effect on body weight.
NCT06105060 **[32]**	RCT For 6 months	NASH (n= 175)	Group1: NAC (2.4 g/day) Orally. Group 2: Rosuvastatin (20	Group3: NAC (2.4 g/day) plus Rosuvastatin (20mg/day) Group4/ control: Vitamin E (400mg b.i.d.)	- improvement of the degree of steatosis and fibrosis. - improvement of oxidative stress, IR, and biochemical related to steatosis	

			mg/day) orally.		and fibrosis.	Not published
NCT05576428 **[33]**	RCT	NAFLD patients with elevated transaminases.	NAC (200mg b.i.d.) plus diet plan and exercise	diet plan and exercise	The antioxidant and anti-inflammatory effect of NAC on improving ALT and AST levels.	Unknown status
NCT05807204 **[34]** (FATHIS)	RCT For 3 months	Males with visceral obesity.	multi-ingredient (L-Histidine, L-Serine, L-Carnosine and NAC) orally	Placebo (maltodextrin)	the effect of daily intake of L-histidine, L-serine, L-carnosine, and NAC, in combination, on the amount of visceral fat, hepatic steatosis, and obesity complications.	Not published
NCT06377631 **[35]** (FATHIS+)	RCT	Postmenopausal females with visceral obesity.	multi-ingredient (L-Histidine, L-Serine, L-Carnosine and NAC) orally	Placebo (maltodextrin)	the effect of daily intake of L-histidine, L-serine, L-carnosine, and NAC, in combination, on the amount of visceral fat, hepatic steatosis, cardiovascular risk, and obesity complications.	Not yet recruiting

FIB-4, fibrosis-4 score; MTF, metformin; NAS, NAFLD activity score; hs-CRP, High Sensitivity C Reactive protein; Il-6, interleukin-6; UDCA, ursodeoxycholic acid; b.i.d., two times a day; t.i.d., three times a day.

Table 3. Summary of included clinical trials reporting the effect of NAC on PCOS as a condition of metabolic syndrome

Trial	Study design	Patient population	Intervention	Comparison	Outcome	Conclusion
Fulghesu et al (2002) **[36]**	Prospective data analysis	PCOS women (n= 37) 6 lean and 31 obese subjects	NAC (1800mg daily) and (3000mg for morbid obesity; BMI> 30 kg/m^2) (n= 31) For 5-6 weeks	Placebo group 6 obese BMI-matched subjects were selected without randomization	The effect of NAC on insulin secretion and insulin sensitivity.	A reduction in Insulin AUC after OGTT and the peripheral insulin sensitivity increased after NAC treatment in hyperinsulinemic subjects**.**
Rizk et al (2004) **[37]**	RCT	CC-resistant women with PCOS (n= 150)	NAC (600 mg b.i.d.) orally plus CC (100 mg daily) from D3 until D7.	Placebo (sugar b.i.d.) orally plus CC (100 mg daily) from D3 until D7.	The insulin-sensitizing effect of NAC as an adjuvant in PCOS women with	A significant increase in both ovulation and PR in the NAC group.

			(n= 75)	(n= 75)	CC resistance.	
Kilic-Okman et al (2004) **[38]**	1 group	PCOS women (n= 20)	NAC (0.6 mg t.i.d.) orally for 4 weeks	----------	The effect of NAC on IR, the lipid profile, and homocysteine levels.	NAC was effective as insulin and testosterone-lowering and improved homocysteine and lipid profile in PCOS
Elnashar et al (2007) **[39]**	RCT	CC-resistant women with PCOS (n= 64)	NAC (600mg t.i.d.) orally for 6 weeks from the 1st day of menses. (n= 32)	MTF (500mg t.i.d.) orally for 6 weeks from the 1st day of the menses. (n= 32)	The effect of NAC and MTF in CC-resistant women with PCOS on hormonal profile and ovulation.	A significant reduction in fasting glucose and fasting insulin levels and an improvement in ovulation rate in the MTF group.
Badawy A et al (2007) **[40]**	Prospective cross-over trial	PCOS women (n= 470) Who failed to ovulate with CC 50-mg, b.i.d. daily for 5 days) starting on D3 of the menses for 1 cycle.	After a washing period of 2 months: CC (50 m, b.i.d. orally for 5 days starting on the 2nd day of the menstrual cycle plus NAC (400 mg, t.i.d.), orally, starting on the 2nd day of the cycle for 5 days.		The adjuvant effect of NAC to CC in induction of ovulation in PCOS women.	The addition of NAC augmented the ovulation.
Masha A et al (2009) **[41]**	Preliminary open study For 6 months	PCOS women (n= 8)	NAC (1.2gm daily, orally) plus arginine "ARG" (1.6 mg daily, 1 vial PO every morning).	----------	- The effect of NAC and ARG combination on ovarian function and some metabolic parameters in PCOS women.	- Long-term treatment with NAC+ARG improves insulin sensitivity represented by improving insulin level and HOMA index. Thus, might restore gonadal function in PCOS.
Abu Hashim H et al (2010) **[42]**	RCT For 3 months The treatment protocol continued for 3 successive menstrual cycles.	CC-resistant women with PCOS (n= 192)	NAC (600mg t.i.d.) orally for 5-6 weeks from the 1st day of menses. (n= 95) At the end of this period, women in both groups received 100 mg CC for 5 days starting from D3 of menses. The dose was increased by 50 mg for the next cycle in case of persistent anovulation.	MTF (500mg t.i.d.) orally for 5-6 weeks from the 1st day of menses. (n= 97)	- The adjuvant effect of NAC and MTF to CC on ovulation, number of follicles, serum levels of estrogen and progesterone, posttreatment endometrial thickness, pregnancy, and miscarriage.	The MTF-CC combination was more significantly effective than NAC-CC combination.
Nasr A (2010) **[43]**	RCT, pilot. 1 year	CC-resistant women with PCOS (n=60)	LOD plus NAC (600mg b.i.d.) orally, for 5 days starting at D3 of the menstrual cycle for 12 consecutive cycles.	LOD plus identical placebo orally, for 5 days starting at D3 of the menstrual cycle for 12 consecutive cycles.	Adjuvant effect of NAC following unilateral laparoscopic ovarian drilling (LOD) for CC-resistant women with PCOS.	A significant increase in both ovulation and PR was in the NAC group.
Oner G et al (2011) **[44]**	RCT	PCOS women (n= 100)	NAC (600 mg, t.i.d.) orally	MTF (500 mg, t.i.d.) orally	- The metabolic and endocrine effect of NAC and MTF	NAC and MTF have a comparable effect on HA and hyperinsulinemia. Their insulin

	For 24 weeks					sensitizer effect didn't relate to TNF-α.
Salehpour et al (2012) **[45]**	RCT	PCOS women (n= 180)	NAC (600mg b.i.d., orally as sachets) plus CC (100 mg daily, orally) from D3 until D7 of the menses. (n= 90)	CC (100mg once, orally) plus placebo (ORS sachets) b.i.d. from D3 until D7 of the menses. (n= 90)	The adjuvant effect of NAC to CC in induction of ovulation in PCOS women	The addition of NAC improved the ovulation and pregnancy rate.
Cheraghi E et al (2014) **[46]**	Randomized pilot study For 6 weeks	Infertile women with PCOS, candidate for ICSI (n= 60) All groups were on ICSI protocol plus the study interventions.	Group 1: a combination of (MTF 500 mg+ NAC 600 mg) t.i.d. (n= 15)	Group 2: Placebo ORS t.i.d. (n= 15) Group 3: MTF 500mg t.i.d. (n= 15) Group 4: NAC 600mg t.i.d. (n= 15)	- The effects of NAC versus MET and their combination on the quality of oocytes and embryos of PCOS women undergoing ovulation induction for ICSI.	-In NAC and NAC+MTF groups, a significant reduction in FF leptin concentrations, FF insulin, LH, and FF MDA levels. -As well as improving oocyte quality in the NAC group compared to placebo. - NAC seems to decrease elevated oxidative stress in PCOS patients.
Maged AM et al (2015) **[47]**	RCT	PCOS women (n= 120) All patients were on CC 50 mg, b.i.d. from day 3 till day 7 of menses.	Group 1: CC + NAC (600 mg, b.i.d.), orally from D3 till D7 of menses	Group 2: CC only, from D3 till D7 of menses Group 3: CC + MTF (500 mg, t.i.d.) continuously	The adjuvant effect of NAC and MTF to CC in induction of ovulation in PCOS women.	- Addition of NAC to CC increased the number of dominant follicles, and ovulation rate and improved the uterine thickness.
Javanmanesh et al (2015) **[48]**	RCT For 24 weeks	PCOS women (n= 94)	NAC 600mg t.i.d. orally (n= 46)	MTF 500 mg t.i.d. orally (n= 48)	- compare the effects of NAC and MTF on some metabolic and clinical symptoms of PCOS.	- No significant difference between MTF and NAC.
Nemati M et al (2017) **[49]**	RCT	CC-resistant women with PCOS (n= 108)	NAC (600 mg, t.i.d.) on the 3rd day of menses, with CC (100 mg once) on D5-9 of the 1st menstrual cycle. For 8 and 12 weeks. (n= 54)	MTF (500 m, t.i.d.) on the 3rd day of menses, with CC (100 mg once) on D5-9 of the 1st menstrual cycle. For 8 and 12 weeks. (n= 54)	- The adjuvant effect of short- and long-term treatment with NAC and MTF to CC on hormonal profile and fertility status in CC resistant.	- MTF and NAC are efficient adjuvant to CC on long-term treatment. - on long-term treatment, NAC and MTF significantly reduced the levels of fasting insulin, SHBG, and FBS.
Fang et al (2024) **[50]**	Pragmatic RCT	PCOS women with anovulation or oligo-ovulation	NAC (600mg t.i.d.) orally from the 2nd to the 4th day of the menses for 5 consecutive days. Then follow	The control group on ovulation induction "OI" protocol using sequential LE and	NAC effect on OI efficacy in women with PCOS.	Significant enhancement of OI efficacy with sequential LE and uFSH in women with PCOS.

		(n= 230)	the same OI protocol as a control group. (n= 115)	FSH. (n= 115)		
NCT02775734 **[51]**	RCT	CC-resistant women with PCOS. (n= 120)	LOD plus NAC (1,200 mg/day) orally for 5 days starting from D2 until D6 of the cycle plus CC (100 mg/day)	LOD plus CC (100mg/day)	Biochemical and Clinical PR, ovulation rate, live birth rate, number of follicles ≥ 18 mm endometrial thickness at ovulation, and incidence of side effects.	Not published
NCT01896492 **[52]**	RCT	Newly diagnosed PCOS females. (n= 200)	NAC (1.2gm/day) plus CC (100 mg/day) from the 3rd day of the cycle till D8.	Placebo plus CC (100mg/day) from 3rd day of the cycle till D8.	The adjuvant effect of NAC to CC in ovulation induction of newly diagnosed PCOS.	Not published

CC, clomiphene citrate; MTF, metformin; FF leptin, follicular fluid leptin; SHBG, sex hormone binding globulin; FBS, fasting blood sugar test; OGTT, oral glucose tolerance test; PR, pregnancy rate; PO, oral route; b.i.d, two times a day; t.i.d, three times a day; uFSH, urinary follicle-stimulating hormone; LH, Luteinizing hormone; ORS, oral rehydration solution; LE, letrozole; LOD, laparoscopic ovarian drilling; ICSI, Intracytoplasmic sperm injection.

4. Discussion

It is well known that oxidative stress and IR are prominent features of metabolic syndrome. Oxidative stress refers to the imbalance between the formation and detoxification of free radical species and ROS.

Throughout the years, the use of strong antioxidants like NAC has been essential in improving oxidative stress and inflammation in metabolic dysfunction. A study by Khoshbaten et al demonstrated that NAC reduced the level of ALT and spleen size with no effect on the degree of hepatic steatosis **[28]**. Similarly, a pilot study of 20 biopsy-proven NASH patients showed a significant reduction in not only ALT but also glucose, insulin, and HOMA-IR index when 1.2 gm of oral NAC combined with 850 to 1000 mg of oral MTF **[27].** A significant reduction in serum levels of AST and GGT was achieved after administration of 1.2 g of NAC for 1 month in the Pamuk et al study as well **[26]**.

Oliveria et al (2008) observed a significant improvement in the degree of hepatic steatosis and fibrosis after 1 year of receiving a combination of NAC and MTF **[27]**. In another study by Oliveria et al (2019), the intention to treat intragroup analysis showed that the combination of NAC and MTF showed an improvement in the degree of steatosis, hepatocyte ballooning, and NAS score **[29]**. In a phase II double-blinded study of biopsy-proven MASLD obese children, the treatment with 600 and 1200 mg of oral NAC ameliorated oxidative stress marker (GSH), inflammatory markers (IL-6 and hs-CRP), IR (HOMA-IR index), and reduced liver stiffness **[31]**.

These findings comply with previous experimental models of NAFLD that demonstrated the capacity of NAC to inhibit lipid accumulation in hepatocytes and lipid peroxidation by modulating FFA signaling and transcriptional factors like SREBP-1c and replenishment of hepatocellular glutathione "GSH" level **[53]**. In addition, preclinical models of NAFLD referred to the improvement of liver function caused by NAC to its ability to reduce the levels of pro-inflammatory and oxidative

stress markers like IL-6, TNF-α, NF-κB, and MDA levels **[54, 55]**. In a pilot study by Garicano et al, the combination of NAC with other elements under the trade name of MetioNac® reduced the risk of MAFLD in patients with metabolic syndrome and FIB-4 <1.3 **[30]**.

Being an insulin-sensitizer, metformin "MTF" is vastly used for the management of IR in PCOS. Long-term administration of MTF may cause gastrointestinal problems, hypoglycemia, vitamin B12 deficiency, and hyperhomocysteinemia. There was a need to use another pharmacological molecule that could manage IR status in PCOS with fewer adverse events. Fulghesu et al was the first clinical study to report the insulin-sensitizing effect of NAC in PCOS management **[36]**. Since then, many studies have compared the effect of NAC with MTF separately or in combination. Cheraghi et al reported a significant reduction in follicular fluid insulin, MDA, and LH levels, thus improving oocyte quality in 60 infertile females with PCOS who were candidates for ICSI when 1.8 g of oral NAC was administered alone or in combination with 1.5 g MTF for 6 weeks **[46]**. In contrast to MTF, which only reduced total cholesterol levels, NAC significantly decreased both total cholesterol and LDL levels **[44]**. This is incompatible with the Javanmanesh study that reported a nonsignificant difference between NAC and MTF on metabolic parameters after receiving 1.8 g of NAC versus 1.5 g MTF for a longer duration (6 months) in larger sample size (94 females with PCOS) **[48]**. Six-month preliminary data showed that long-term treatment with the combination of NAC and arginine may restore gonadal in PCOS by lowering insulin levels and HOMA-IR index **[41]**.

Clomiphene citrate (CC) is considered the drug of choice for ovulation induction in PCOS women. Up to 40% of PCOS women using CC may have clomiphene resistance which is known as failure to ovulate following a 150 mg daily dose of CC for 5 days per cycle, for at least three cycles. IR, obesity, and HA contribute to CC- --resistance by preventing the response of ovaries to elevated endogenous FSH levels after CC treatment. The adjuvant effect of NAC to CC either in PCOS women with or without CC resistance was demonstrated by many studies. Rizk et al (2004) and Salehpour et al (2012) reported that the addition of NAC to CC in PCOS women with or without CC-resistance respectively resulted in a significant increase in ovulation and pregnancy rates compared to placebo **[37, 45]**. Similarly, a prospective cross-over trial of 470 PCOS females who failed to ovulate following CC treatment for one cycle showed that the addition of NAC enhanced ovulation **[40].** Maged et al (2015) and Nemati et al (2017) evaluated the adjuvant effect of NAC and MTF on CC and concluded that both NAC and MTF are efficient adjuvants to CC and have a positive impact on IR, HA, endometrial thickness, and pregnancy rate **[47, 49]**. On the other hand, Elnashar et al (2007) and Abu Hashim et al (2010) reported that MTF with CC combination is more effective for the induction of ovulation than NAC with CC combination **[42, 39]**.

Laparoscopic ovarian drilling (LOD) is one of the strategies used to confer CC- resistance, receiving 1.2 gm daily for 5 consecutive days starting from D3 of the cycle after LOD for 1 year increased ovulation and pregnancy rates **[43]**. Kilic-Okman et al showed that 1.8 mg of NAC for 4 weeks can reduce homocysteine, insulin, and testosterone levels and may be used to ameliorate homocysteine levels in patients with PCOS **[38]**. Compared with MTF, NAC has been reported to be well-tolerated with fewer side effects adjuvant to CC in women with PCOS **[44, 46, 47, 48, 49]**. The lack of precise statistics about NAC side effects may be due to the brief

monitoring period. Thus, research is required to assess NAC's long-term safety and effectiveness in PCOS-affected women.

Multiple ongoing trials aim to assess the impact of different doses of NAC on different metabolic parameters associated with MAFLD or PCOS. The study under registered number NCT06105060 will use a high dose of NAC for 6 months versus rosuvastatin (20 mg/day), Vitamin E (800 mg /day), and NAC plus rosuvastatin to investigate the improvement of biochemicals related to liver steatosis and fibrosis **[32]**. The antioxidant effect of NAC on improving ALT and AST serum levels will be assessed in NAFLD patients with elevated transaminases **[33]**. Both FATHIS and FATHIS+ aim to evaluate the effectiveness of the combination of NAC, L-histidine, L-serine, and L-carnosine in the amount of visceral fat, hepatic steatosis, and cardiovascular risk related to obesity in males and postmenopausal females with visceral obesity, respectively **[34, 35]**. Regarding PCOS, the registered NCT02775734 study will investigate the efficacy and safety of NAC in PCOS females with CC resistance when combined with CC and LOD versus CC plus LOD **[51]**. In contrast to other studies that evaluate the NAC additive effects on CC in the case of CC resistance, NCT01896492 will investigate the adjuvant effect of NAC on CC in newly diagnosed PCOS females **[52]**.

Conclusion

Evidence mentioned in this review supports the beneficial impact of NAC on oxidative stress status, IR, and HA which are considered the main contributors of MAFLD and PCOS. Since NAC lowers the level of some metabolic parameters such as insulin, total cholesterol, LDL, FF LH, FF MDA, and pro-inflammatory markers, it increases the maturity of oocytes in PCOS and inhibits lipid accumulation in NAFLD pre-clinical models. Being a safe, well-tolerated antioxidant with insulin-sensitizing and anti-apoptotic properties, NAC may be used as an add-on or alternative therapy in PCOS and MAFLD.

Recommendations

Further RCTs with a large sample size and longer follow-up periods are needed to confirm the therapeutic effectiveness of NAC in PCOS, NAFLD, and other metabolic disorders.

List of abbreviations

Mets, metabolic syndrome; T2DM, type II diabetes mellitus; IR, insulin resistance; MAFLD, metabolic dysfunction- associated fatty liver disease; PCOS, polycystic ovary syndrome, NAC, N acetylcysteine; HCC, hepatocellular carcinoma; FFA, free fatty acids; DNL, de novo lipogenesis; NASH, non-alcoholic steatohepatitis; SREBP-1c, sterol regulatory element-binding protein-1c; ROS, reactive oxygen species; HA, hyperandrogenism; SHBG, sex hormone binding globulin; IGF-1, insulin-like growth factor-1; NF-κB, nuclear factor-kappa B; SH, thiol group; MeSH, Medical Subject Heading; PRISMA, preferred reporting items for systematic review and meta-analysis; RCT, randomized controlled trials; UDCA, ursodeoxycholic acid.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Participate

Not applicable.

Consent for publication

Not applicable.

Availability of the data and Material

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare that there is no conflict of interest.

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