

Higher Expression of miR-155 and miR-103 in Patients with Gitelman Syndrome: Potential Implications for Angiotensin II-Induced Cardiovascular Remodeling in Hypertension

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Keywords

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Abstract

Introduction: miR-155 and miR-103 are multifunctional miRNAs known to be involved in angiotensin II (Ang II) signaling linked with hypertension and cardiovascular remodeling, although their role is controversial and not completely clarified. Gitelman syndrome (GS), rare genetic tubulopathy, represents a human model of an endogenous Ang II signaling antagonism and GS patients are in fact protected from Ang II-mediated cardiovascular remodeling. This study aimed to compare the expression of miR-155 and miR-103 in patients with GS vs. healthy controls. **Methods:** Sixteen patients with GS and 21 age- and sex-matched healthy controls were recruited from an active cohort at the Nephrology Unit of Padua University Hospital and among volunteers, respectively. The specific miRNA population was isolated from plasma, and miR-155 and miR-103 were then quantified using droplet PCR and TaqMan miRNA assays and compared using the Mann-Whitney U test. **Results:** In GS patients, expression of miR-

155 (528.7 vs. 64.40 copies/sample, $p = 0.0015$) and miR-103 (80.25 vs. 23.94 copies/sample, $p = 0.0034$) were significantly higher compared to the control group. **Conclusion:** This is the first study investigating circulating miRNAs in GS patients. The difference in expression levels of miR-155 and miR-103 in these patients compared to healthy subjects suggests that these miRNAs may be associated with mechanisms contributing to their well-established protection from Ang II-mediated cardiovascular remodeling.

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Introduction

Gitelman syndrome (GS) is a genetic tubulopathy caused by the biallelic inactivation of *SLC12A3* gene, encoding for sodium chloride cotransporter. The prevalence of GS is 1:40,000 worldwide [1, 2]. It is characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, sodium wasting and, despite hyperreninemia and hyperaldosteronism, normo/hypotension, and absence of cardiovascular remodeling [3]. In hypertension, remodeling of cardiac left ventricle, alterations in the morphology and mechanical properties of the vasculature

are mostly driven by angiotensin II (Ang II) through the Ang II type 1 receptor (AT1R) signaling pathway, leading to vasoconstriction, inflammation, oxidative stress, fibrosis, and endothelial dysfunction [3, 4].

In the past, several mechanisms behind the lack of Ang II-induced cardiovascular remodeling in GS (and Bartter's syndrome) patients have been attributed to the blunted activation of AT1R intracellular signaling pathways and have provided novel insights into the RAAS signaling pathways [3]. More specifically, the intracellular mediator RhoA/Rho kinase is expressed at lower levels in patients with GS compared to healthy subjects [3, 5]. On the other hand, there is a greater activation of the counterregulatory arm of the RAAS system, namely, the AT2R/MasR signaling pathways [3, 5]. Additionally, it was observed that GS patients show a reduced reactive-oxygen-species-mediated intracellular response to Ang II, with lower levels of p22^{phox} and higher expression of HO-1, together with lower levels of TGF- β compared to controls [3, 5]. All together, these altered pathways determine decreased vasoconstriction, oxidative stress, fibrosis, and overall cardiovascular remodeling, making GS patients a human model of endogenous Ang II antagonism, opposite to that of hypertension [3, 5].

miRNAs are non-coding nucleotides of approximately 22 bp that bind to the 3'UTR of mRNAs to undergo biogenesis inhibition or mRNA degradation, ultimately affecting gene expression [6, 7]. Given the central role of Ang II signaling in cardiovascular remodeling, miRNAs modulating this pathway are of particular interest, like hsa-miR-155 (miR-155) and miR-103 [6, 7]. miR-155 is a highly conserved non-coding single-stranded RNA encoded by the B-cell integration cluster gene located on chromosome 21 and is expressed mostly in hematopoietic cells, but also in fibroblasts, epithelial tissues, reproductive tissues, and the central nervous system [6]. miR-155 is involved in multiple biological processes, including inflammation, immunity, cell proliferation and apoptosis, vascular homeostasis, hypertension, cardiovascular remodeling, and tumorigenesis [6, 8]. Studies on this multifunctional miRNA pointed out its complexity, especially in cardiovascular pathophysiology [6, 8, 9]. Papadopoulos et al. had already hypothesized a role of miR-155 in GS [8], and miR-155 levels were found to be inversely associated with diastolic and systolic blood pressure in a hypertensive cohort [10].

miR-103 is a member of the miR-103/107 family located on human chromosome 5 [11]. It is expressed by several cell lines and acts as an oncogenic miRNA,

promoting cell proliferation (non-small lung cancer, breast, colon, squamous cell carcinoma). This miRNA family also plays a role in hypertensive nephropathy, cardiovascular remodeling, oxidative stress, and metabolic disease [11–13]. So far, there is just one report about miRNAs in GS, which only includes miRNAs in urinary vesicles and kidney tissue [14]. The aim of our comparative case/control study was to evaluate the miR-155 and miR-103 expression in the plasma of GS patients, human model of endogenous Ang II antagonism, the opposite of hypertension, compared to healthy subjects.

Patients and Methods

Patients

Sixteen GS patients, genetically and biochemically characterized, 6 males, mean age 43.22 ± 14.28 years, were recruited from the cohort in active follow-up at the Nephrology Unit of Padua University Hospital. All of these patients showed clinical signs of GS including hypokalemia with metabolic alkalosis, hypomagnesemia, normo/hypotension despite high Ang II levels and requiring potassium and magnesium supplements. Twenty-one age- and sex-matched healthy controls, 8 males, mean age 45.03 ± 11.91 years volunteered for the study from the personnel of the Nephrology Division of Padua Hospital. Exclusion criteria for both GS and controls were current infection, diagnosis of hypertension and treatment with antihypertensive drugs, current treatment with corticosteroids, and diabetes.

The number of participants was initially estimated based on the study by Kok et al. [15], which reported that approximately 19 subjects per group are sufficient to detect biologically and clinically relevant differences in miRNA expression (fold change ~ 1.5) in cardiovascular diseases with a more than 80% average power. However, having a final sample size of 16 GS patients, the statistical adequacy of the sample size was verified by performing a post hoc sensitivity analysis using G*Power (version 3.1.9.4) for a two-sided Wilcoxon-Mann-Whitney test, with $\alpha = 0.05$ and power $(1-\beta) = 0.80$.

Methods

Plasma was isolated from blood by centrifuging at 3,000 rpm for 10 min at 4°C within 1 h of collection in order to preserve RNA integrity. Total RNA (including miRNAs) was isolated from plasma using “miRNeasy Serum/Plasma Kit” (Qiagen, Milan, Italy) following manufacturer instructions. Starting from 10 ng of total

RNA, the specific miRNA population was then reverse-transcribed and pre-amplified using TaqMan Advanced miRNA cDNA Synthesis Kit (Cod. A25576, Thermo-fisher Scientific, Milan, Italy), according to manufacturer instructions.

The absolute quantification of miR-155 and miR-103a (miR-103) was obtained using a Digital Droplet PCR system (ddPCR) (Bio-Rad Laboratories, Segrate, Italy). cDNAs were combined with the specific mix containing primers and probes (hsa-miR-155-5p, Assay ID. 483064_mir; hsa-miR-103a-3p, Assay ID 478253_mir, Thermo-fisher Scientific, Milan, Italy), and ddPCR Supermix for Probes (no dUTP) (Cod. #1863024, Bio-Rad Laboratories, Segrate, Italy) and were converted into droplets with the QX200™ Automated Droplet Generator (Bio-Rad Laboratories, Segrate, Italy). Droplet-partitioned samples were transferred to a 96-well plate, and PCR was performed using the Bio-Rad C1000™ (Bio-Rad Laboratories, Segrate, Italy) with the following protocol: 95°C for 5 min, followed by 45 cycles of 95°C for 30 s and 55°C for 1 min, with a final step of 98°C for 10 min. Droplet Digital PCR data were analyzed with QuantaSoft analysis software (Bio-Rad Laboratories, Segrate, Italy). Absolute levels of the target miRNAs were expressed as number of copies per sample analyzed in duplicate.

Statistical Analysis

Data were expressed in mean $\pm$ SD or median and interquartile range (IQR) depending on their distribution. The Mann-Whitney U test was used to compare miRNA data from the two populations given their non-normal distribution. The Hodges-Lehmann estimator with 95% confidence intervals was calculated to quantify the magnitude of the effect. Statistical significance was set at $p < 0.05$. The statistical analysis was performed with GraphPad Prism 10 software for macOS (GraphPad Software, San Diego California, USA).

Results

Nearly all 16 GS patients carried pathogenic *SLC12A3* mutations in compound heterozygosity, except for 3 patients who carried only one mutation (single heterozygote), despite presenting with clinical and biochemical signs of GS. Table 1 displays the pathogenic variants carried by every patient and the respective allelic status. Interestingly, none of the patients was a homozygous carrier of *SLC12A3* mutations. Overall, 5 patients

were consanguineous (3 belonging to one family and 2 belonging to another family).

In the GS group, the median number of copies per sample of miR-155 was 528.7 with an IQR of 573.2, while in healthy subjects, 64.40 number of copies/sample with an IQR of 322.0. The Hodges-Lehmann estimate of the median difference was 238.8 copies/sample (95% CI: 72.4–575.1).

The number of copies/sample was higher in the GS group compared to healthy subject group, with a statistically significant difference ($p = 0.0015$) as shown in Figure 1. Regarding miR-103, the median number of copies/sample in the GS group was 80.25 copies/sample, with an IQR of 94.43, while in the control group it was 23.94 copies/sample with an IQR of 38.98 copies/sample and a Hodges-Lehmann median difference of 51.37 copies/sample (95% CI: 13.39–80.61).

The sensitivity analysis indicated that, with the available sample size ($n = 16$ vs. $n = 21$), the study was powered to detect an effect size of approximately Cohen's $d = 0.98$. Figure 1 shows that, in the GS group the expression of miR-103, was statistically higher than in the control group ($p = 0.0034$).

Discussion

Our study demonstrates that GS patients show a higher plasma expression of both miR-155 and miR-103 compared to healthy controls. These data, added to blunted Ang II signaling, normo/hypotension, and lack of cardiovascular remodeling despite high Ang II levels, that characterize this syndrome, may indirectly provide further information on the roles of these miRNAs in hypertension and cardiovascular remodeling in humans.

Vascular Effects

In primary cultured mice vascular smooth muscle cells, miR-155 counteracts Ang-II-induced increase in cell viability and proliferation [16]. miR-155 was also demonstrated to decrease AT1R gene and protein expression in mice and rats [16, 17]. Moreover, Ang-II-induced ERK1/2 phosphorylation was reduced in rats' adventitial fibroblasts incubated with miR-155 vs. controls, suggesting an efficacious suppression of Ang II biological effects through miR-155 [17]. This effect was ascribed to the downregulation of AT1R [17]. Accordingly, previous studies performed by our group revealed that fibroblasts from patients with GS (and Bartter's syndrome) exhibited a shorter duration of the Ang II-induced increase in ERK1/2 phosphorylation compared

Table 1. Variants carried by GS patients recruited in the study

Patient	Variant (cDNA)	Protein translation	Allelic status
1	c.514T>C Possible deletion of exons 24 and 25	p.Trp172Arg	Compound heterozygous
2	c.2947G>A (in trans) with c.2951+6T>C c.3070G>A	p.Val983Ile p.? p.Val1024Met	Triple compound heterozygous
3	c.2049G>A	p.Gly675Asp	Single heterozygous
4	c.1948G>A	p.Gly650Arg	Single heterozygous
5	c.2985G>A c.2089_2095delACCAAGT	p.Cys994Tyr p.Thr697fs	Compound heterozygous
6	c.2985G>A c.2089_2095delACCAAGT	p.Cys994Tyr p.Thr697fs	Compound heterozygous
7	c.644T>C c.1763C>T	p.Pro215Leu p.Ala588Val	Compound heterozygous
8	c.1948G>A	p.Gly650Arg	Single heterozygous
9	c.1948G>A c.1180+1G>T	p.Gly650Arg	Compound heterozygous
10	c.1924C>G c.2981G>A	p.Arg642Gly p.Cys994Tyr	Compound heterozygous
11	c.457G>A c.1181G>A	p.Val153Met p.Gly394Asp	Compound heterozygous
12	c.2581C>T c.2935_2942delGCTGCTCT	p.Arg861Cys p.Ala979Hisfs*66	Compound heterozygous
13	c.1181G>A c.1925G>A	p.Arg642His p.Gly394Asp	Compound heterozygous
14	c.2039delG c.2981G>A	p.Gly680Aspfs*21 p.Cys994Tyr	Compound heterozygous
15	c.1196_1202dup7bp c.2981G>A	p.Ser402X p.Cys994Tyr	Compound heterozygous
16	c.1489A>T c.2981G>A	p.Lys497 p.Cys994Tyr	Compound heterozygous

to healthy subjects' fibroblasts [3]. This was explained by RGS-2 upregulation [3, 5], which attenuates AT1R/Gαq signaling and favors AT2R-mediated pathway. While in hypertensive patients RGS-2 expression is reduced [3, 5], GS patients show an increased expression of RGS-2 and its silencing restores a hypertensive-like Ang II response [3, 5]. Intriguingly, the increased expression of miR-155 found in GS patients might contribute to the upregulation of RGS-2 in GS patients and also explain the similar AT1R/AT2R protein levels in GS and controls [3]. Although miR-155 has been reported to reduce eNOS expression [18], AT2R/NO signaling appears indirectly enhanced by miR-155 [8], supporting its role in the vasorelaxation typical of GS patients [3, 5]. To-

gether, these mechanisms demonstrate Ang II antagonism in GS and Bartter's syndrome. Moreover, they were also proposed as contributors to protection against severe SARS-CoV-2 infection [8], which was coincidentally demonstrated in GS and Bartter's syndrome patients [19].

Oxidative Stress

Indirectly, miR-155 positively regulates the expression of HO-1 and overall reduces oxidative stress [8]. miR-103 showed a mutual relationship with H₂O₂ in human umbilical vein endothelial cells: H₂O₂ exposure reduced miR-103 expression, while, in turn, overexpression of miR-103 increased cell viability and reduced apoptosis

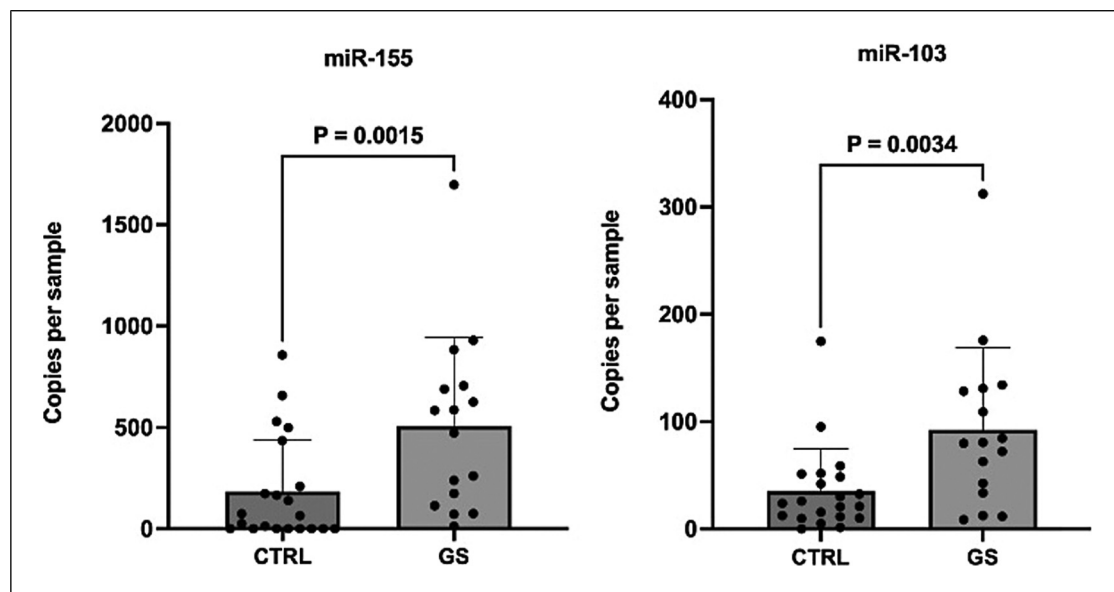


Fig. 1. Bar plot showing differential expression of miR-155 and miR-103 in controls vs. GS patients. Given the non-normal distribution of the data, Mann-Whitney U test was used for the statistical analysis. Statistical significance was set at $p < 0.05$.

rate and production of reactive oxygen species [13]. These findings corroborate the fact that GS patients show a higher expression of HO-1 and reduced oxidative stress [3].

Fibrosis and Inflammation

In human subjects, miR-155 expression showed a negative correlation with that of TGF- β [10]. In light of this evidence, higher levels of miR-155 might contribute to explaining the lower expression of TGF- β and Rho kinase found in GS patients [3]. Consistently, miR-155 overexpression completely suppressed TGF- β -induced endothelial to mesenchymal transition in mouse embryonic endothelial cells and reduced RhoA levels [20]. By contrast, in mouse endothelial cells miR-103 was discovered to act in the regulatory axis of Ang-II-induced renal inflammation and fibrosis through an increase in NF κ B expression, by downregulating SNRK [12]. Blood and urine miR-103 levels were higher in hypertensive patients than in healthy subjects and correlated with albuminuria [12]. Of note, the same study reported that Ang II increases miR-103a-3p expression independently of arterial pressure [12]. While these findings support a link between miR-103 and Ang II-related pathways, they also underscore the controversial role of this miRNA, reflecting the fact that its effects might be both detrimental and potentially compensatory

depending on the context. In this framework, the elevated miR-103 levels in our GS cohort might reflect increased Ang II levels; however, it is possible – but still speculative – that the concomitant RGS-2 mediated attenuation of AT1R signaling contributes to limiting downstream pathological consequences, including hypertension and Ang-II-induced cardiovascular damage.

Cardiac Remodeling

In animal models, miR-103 was found to inhibit cardiac hypertrophy [11], which is in agreement with the observation that GS (and Bartter's syndrome) patients do not show signs of left ventricular hypertrophy compared to controls and hypertensive subjects [3, 5].

Insulin Resistance/Sensitivity

The relationship between GS and insulin sensitivity/resistance is still debated [1–3, 5, 21]. In animal models, the role of miR-155 is also controversial in insulin resistance [22, 23], while miR-103 acts as a negative regulator of insulin sensitivity [24].

The only report about miRNAs in GS has recently been published by Chen et al. and consisted of a case-control comparison of miRNAs in urinary extracellular vesicles and kidney tissue [14], which are not directly comparable with plasma miRNAs [25]. miR-155 levels were similar in the two groups, while miR-103 was

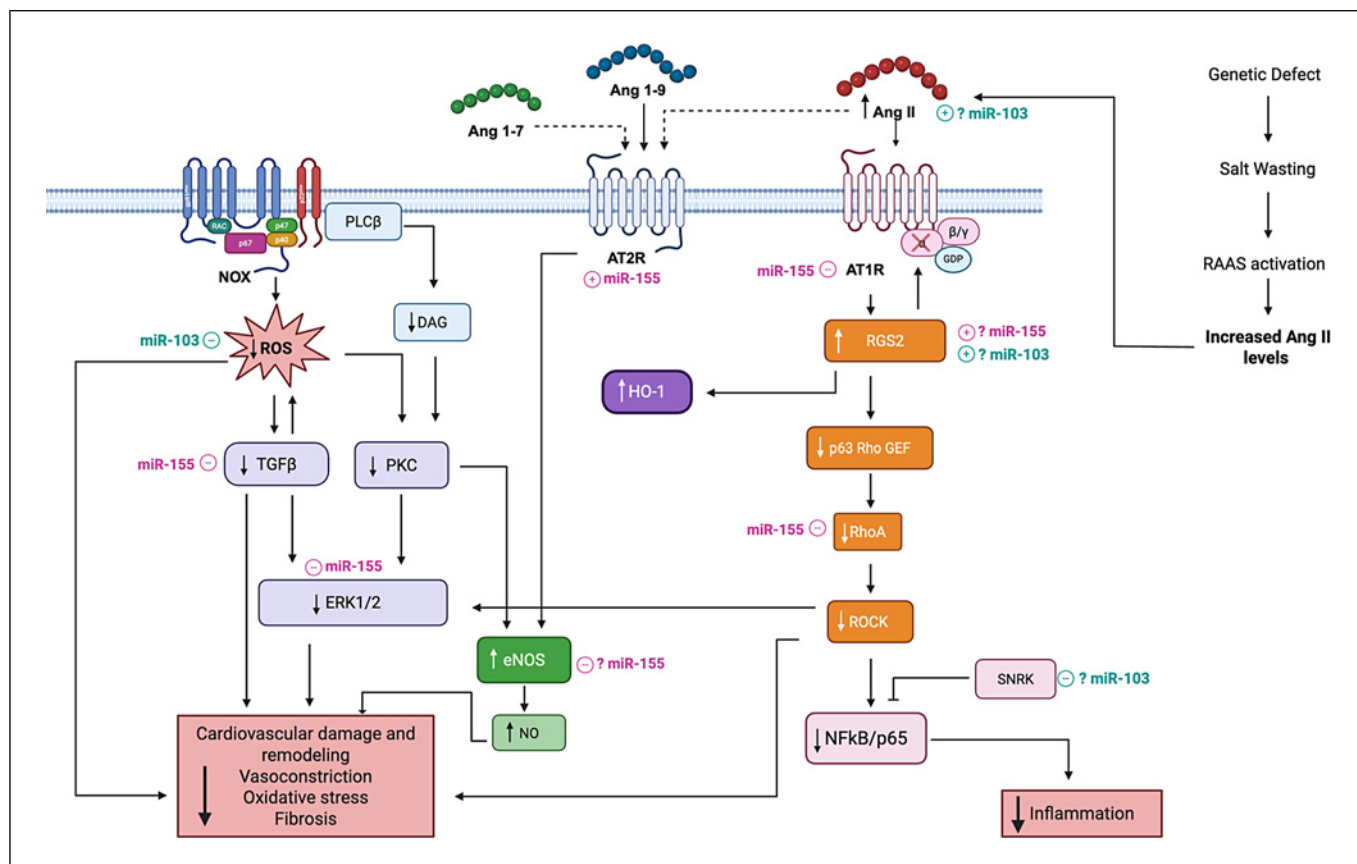


Fig. 2. Hypothetical role of miR-155 and miR-103 in the Ang II blunted pathway in GS. The figure depicts the blunted AT1R signaling pathway in GS. We present the hypothesis that miR-155 and miR-103 might indirectly increase RGS-2 levels, thereby regulating the G-protein activation and the RhoA-ROCK signaling in GS, together with the downregulation of RhoA by miR-155. Based on previous in vitro/animal models, miR-155 might play a role in the down-regulation of AT1R and in the reduced phosphorylation of ERK1/2 that have been observed in GS. We

also propose the role of miR-155 in GS in promoting the counterregulatory AT2R cascade, thereby increasing NO production and thus inducing vasorelaxation, as supported by previous studies. Moreover, miR-155 might be involved in explaining lower TGF-β levels and lower ROS production in GS. + → up-regulation (based on previous in vitro/animal studies); - → downregulation (based on previous in vitro/animal studies); +? → hypothetical upregulative role; -? → hypothetical downregulative role.

downregulated in GS vs. controls in kidney biopsies ($p = 0.04612$), but not in urinary extracellular vesicles, highlighting the tissue-specific nature of miRNA expression. Notably, hsa-let7d-3p was upregulated in GS and shown to inhibit NEDD4L, a key regulator of ENaC degradation, suggesting a role in modulating tubular ENaC expression in GS [14].

So far, only therapeutics based on miR-155 antagonists have been developed for T-cell leukemia/lymphoma [7]. On the other hand, promoting the expression of miR-155 was proposed as a strategy to regulate blood pressure in hypertension [16]. However, current evidence points out to the dual and context-dependent role of miR-155 in cardiovascular diseases, showing both protective and potentially

harmful effects. In hypertension and Ang II-related pathways, it can attenuate damage by downregulating AT1R and inflammatory signaling but may also promote endothelial dysfunction via eNOS inhibition. Moreover, evidence is mostly based on in vitro and animal models, while human data are limited and mainly associative [7]. We also lack robust mechanistic insights from human studies about the role of miR-103 in cardiovascular and kidney disease. Being a model of endogenous Ang-II antagonism, miR-155 and miR-103 data in GS patients vs. healthy controls provide new helpful perspectives into the topic (Fig. 2).

A limitation of this study is that Ang II, RGS-2, AT1R, AT2R, and other AT1R pathway mediators' levels were not directly assessed in the two cohorts of this study, and

therefore, mechanistic conclusions cannot be drawn; our speculations are based, in fact, on prior findings of our studies in comparable GS populations. However, studies are ongoing to better define the role of these miRNAs in Ang II signaling in GS. Another limitation is the small sample size, which is, however, justified by the rare nature and low prevalence of the disease. Despite this, sensitivity analysis demonstrated that the study retained sufficient power to detect large effect sizes, and the corresponding confidence intervals support the magnitude and robustness of the observed differences. Finally, although ddPCR allows reliable absolute quantification of circulating miRNAs, the lack of normalization using spike-in controls or endogenous reference miRNAs should be considered a methodological limitation.

In conclusion, to our knowledge, this is the first study investigating circulating miRNAs in patients with GS. The differential expression of miR-155 and miR-103 in GS compared to healthy subjects suggests a potential association between these miRNAs' levels and the GS phenotype, which is characterized by protection from Ang II-mediated cardiovascular remodeling. Although further studies are warranted, these initial findings on miR-155 and miR-103 may provide a rationale for exploring miRNA-based therapeutics strategies aimed at modulating Ang II-related cardiovascular damage in hypertension.

Statement of Ethics

The study protocol was reviewed and approved by the Ethical Committee of the Padua University Hospital, Approval No. AOP3061, and written informed consent was obtained from all study participants.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization and writing – original draft: M.C. and L.A.C. Data curation and investigation: M.C., I.C., G.D., and L.A.C. Methodology: M.C., I.C., and G.D. Formal analysis: M.C., I.C., G.D., and P.A.D. Resources: F.N. and L.A.C. Writing – review and editing: L.A.C. and P.A.D. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author (L.A.C.) or the first author (M.C.).

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