

## The Mona Lisa Decrypted: Allure of an Imperfect Reality



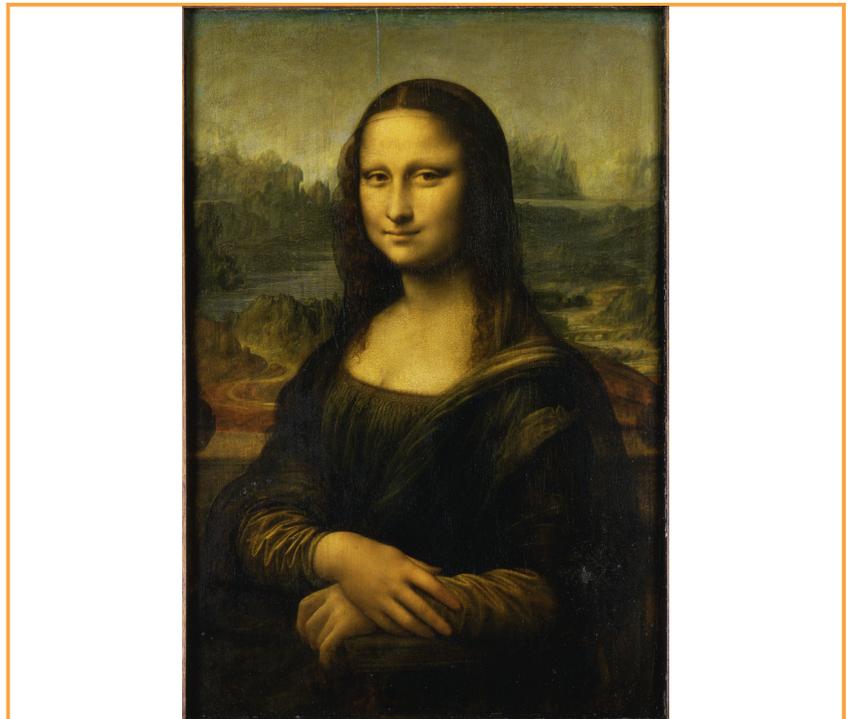
**To the Editor:** The iconic portrait of Lisa Gherardini, the enigmatic *Mona Lisa*, has endured centuries of fascination by artists, scholars, medical professionals, and even thieves.<sup>1</sup> A wealthy silk merchant in Florence, Italy, Francesco del Giocondo commissioned Leonardo da Vinci to produce this masterpiece of his wife following the birth of their child, Andrea, in 1502.<sup>2</sup> Although evidence is fragmentary, general belief is that work on the painting began in 1503. Subsequently, the painting was taken to France in 1516, completed there, and adorned the court of King Francis I until its permanent display in the Louvre in 1797 (Figure).

The *Mona Lisa*, also referred to as *La Gioconda* (or *La Joconde*), attracted medical attention in 2004 when a team of rheumatologists and endocrinologists pointed to the presence of potential cutaneous abnormalities captured in the stunningly detailed portrait that suggested the presence of a lipid disorder. Dequeker et al<sup>3</sup> suggested that the skin lesions noted on the inner end of the left upper eyelid were highly suggestive of xanthelasma and the swelling depicted on the dorsum of the right hand, resting upon the left, was consistent with a subcutaneous lipoma. These findings led them to postulate the connection between hyperlipidemia and consequent ischemic heart disease, which may have led to Gherardini's demise. Thus, they defined this observed constellation to consist of a possible familial form of hyperlipidemia leading to premature atherosclerosis. In their excellent work, these authors also point to the possibility that the mysterious smile may have been a residual of a Bell's palsy. Arguments that reduce compatibility with a familial or genetic

cause of the disorder include the absence of corneal arcus or an extensive family history of premature death. Importantly, Lisa Gherardini (1479-1542) lived to be 63 years of age (not 37 years of age as has been erroneously reported<sup>3</sup>), and it would have been unusual, if not impossible, to see her advance to that age in the presence of untreatable premature atherosclerosis from a genetically driven hyperlipidemia.<sup>4</sup> We believe that a more unifying diagnosis, that of clinical hypothyroidism, is evident and more likely in this uncannily detailed portrayal.

The painting suggests a yellowish discoloration of the skin, which is known to occur in hypothyroidism because of impaired hepatic conversion of carotene to vitamin A, resulting

in excess deposition of serum carotene in the stratum corneum.<sup>5</sup> The black veil that hangs below what appears to be a large forehead indicates a receding hair line, with hair that appears to be thinned. A complete lack of eyebrows or other hair throughout the pale skin further supports this diagnosis, and cascading hair down the side appears coarse in character.<sup>6</sup> Curiously, a close look at the neck does insinuate the possible presence of a diffuse enlargement such as a goiter. The xanthelasma could certainly represent a secondary hyperlipidemia, and swelling in the dorsum of the right hand may be a xanthoma or a lipoma, further supporting the presence of a systematic metabolic dyslipidemia as often noted in advanced stages of hypothyroidism.



**FIGURE.** *Mona Lisa* (circa 1503-1506). Oil on panel, 77 × 53 cm (30 × 21 in). René-Gabriel Ojéda. Musée Du Louvre, Paris, France (with permission, Art Resource, New York, NY). Note the high forehead, thinned and coarse hair, absent eyebrows, xanthelasma at the left medial canthus, swelling on the dorsum of the right hand, suggesting a lipoma or xanthoma, and overall yellowish hue of the skin. Importantly, note the absence of corneal archus and presence of possible goiter in the region of the thyroid.

**TABLE. Thyroid Swellings Depicted in Italian Renaissance Art<sup>a</sup>**

Painting	Painter	Comment
<i>Crucifixion of Saint Andrew</i>	Caravaggio 1607	A poor old lady with a goiter, on left lower part of painting
<i>Judith and her Maidservant</i>	Artemisia Gentileschi 1613	The main character depicted with an obvious large thyroid swelling
<i>Transfiguration of Christ</i>	Raffaello 1516	A boy "possessed" with exophthalmos and neck swelling, possibly representing a toxic goiter, is shown in the right corner
<i>Christ after flagellation</i>	Diego Velazquez 1626	Young boy with a large goiter, on the right hand of painting
<i>The Resurrection</i>	Piero della Francesca 1460	A sleeping soldier with a clear thyroid enlargement that could be a thyroglossal cyst

<sup>a</sup>Selected data compiled from *Am J Surg*,<sup>11</sup>.

In this circumstance, if Lisa Gherardini was indeed suffering from severe hypothyroidism or its consequences, the mysterious smile may at one level be representative of some psychomotor retardation and muscle weakness leading to a less than fully blossomed smile. An even more intriguing diagnosis could suggest the presence of hypothyroidism in concordance with primary biliary cirrhosis.<sup>7</sup> The later diagnosis has been posited by some authors, but association with hypothyroidism was not postulated.<sup>8</sup> However, we believe that the answer may be simpler and epidemiologically supported as a postpartum hypothyroidism.

There are at least 2 distinct natural history-supporting data that support this diagnosis of hypothyroidism. First, during the Renaissance period, eating habits in Italy were primarily vegetarian, based on cereals, root vegetables, and legumes, and with little meat, as opposed to dietary patterns in Northern Europe where livestock was more developed. Seafood was uncommon inland and famine was common, because harvest was often scarce, with only 16 full harvest seasons from 1375 to 1791 in the Tuscany region.<sup>9</sup> Thus, the diet was one that was often iodine deficient and more importantly, the eating habits promoted the development of goiters. As early as 1959,

Keele<sup>10</sup> postulated that the Mona Lisa had a "puffy neck," suggesting a goiter. Evidence of this is noted in several works of art during that period wherein figures are often depicted with goiters. Sterpetti et al<sup>11</sup> studied thyroid swellings in the art of the Italian Renaissance and concluded that such depictions were very common and were the most prevalent pathological condition shown in Byzantine artworks, noting 70 paintings and 10 sculptures with a thyroid swelling (we adapt a few examples from this work in the [Table](#)). As a contemporary example, in 1999, the Pappano population-based study in Italy concluded that in this southern Italian population, the prevalence of a goiter was 59.8% in adults, suggesting that it is still a problem of agricultural rural populations even in modern times.<sup>12</sup> The second important evidence supporting the theory that Lisa Gherardini had hypothyroidism is the fact that she had given birth to her male child, Andrea, recently within months before sitting for the painting.<sup>2</sup> It is possible that she suffered from a subclinical presentation of peripartum thyroiditis, with an early manifestation of hyperthyroidism eventually setting into a chronic phase of hypothyroidism.<sup>13</sup> This, coupled with the living conditions

and iodine-deficient diet of this period in the Florentine region, would have characteristically led to the secondary manifestations of underlying hypothyroidism.

Although we have attempted to provide a unifying hypothesis for the *Mona Lisa*, we admit that the truth may lie elsewhere. A possibility for the loss of facial and bodily hair may be in intentional depilation, which was practiced in those times, with techniques catalogued in *Gli Experimenti* by Caterina Sforza during the Italian Renaissance.<sup>14</sup> The yellowish discoloration may represent age-related changes (perhaps from the use of varnish, which may yellow over time) rather than an original depiction as such. The smile may be due to da Vinci's experiments with a technique called sfumato, which allows tones and colors to fade into each other without discrete lines like smoke or blurred dimensions.<sup>15</sup> Certainly, we should also admit that our unifying theory may be as plausible as the multiple explanations provided, each open to individual and collective bias. In summary, we believe that the enigma of the *Mona Lisa* can be resolved by a simple medical diagnosis of a hypothyroidism-related illness that could have been the result of a peripartum thyroiditis accentuated by the living conditions of the Renaissance. In many ways, it is the allure of the imperfections of disease that give this masterpiece its mysterious reality and charm.

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## Radiofrequency Ablation Therapy for Large Benign Thyroid Nodules



**To the Editor:** We read with great interest a report by Hamidi et al,<sup>1</sup> titled "Outcomes of Radiofrequency Ablation Therapy for Large Benign Thyroid Nodules: A Mayo Clinic Case Series." Hamidi et al<sup>1</sup> presented a retrospective

review of 14 patients with predominantly solid thyroid nodules (TNs) treated with radiofrequency ablation (RFA) at the Mayo Clinic. The authors achieved 44.6% of median volume reduction with 8.6 months of the median follow-up period. The clinical efficacy was proved by resolution of compressive symptoms and improvement of cosmetic concerns. There were minor complications (21%) and no reported major complications. They concluded that RFA has an acceptable safety profile and should be considered as a low-risk alternative to conventional treatment of symptomatic benign TNs.

We congratulate the authors for their meaningful results. Perhaps most importantly, this is the first research reporting the experience of thyroid RFA from the United States. We are certain that this research will be meaningful for both physicians and patients within the United States.

However, several factors should be considered in technical and clinical aspects to achieve sustainable results in the future. The research enrolled large-sized TNs (mean volume, 24 mL). These results were may be induced by using the standard RFA techniques, the transisthmic approach and the moving-shot technique, which are recommended by current RFA guidelines.<sup>2</sup> In addition, the authors used general anesthesia. However, most of the previous RFA studies used local anesthesia in the perithyroidal area because sensory nerves are present in the perithyroidal area (not inside the thyroid gland).<sup>3</sup> Therefore, pain during RFA is tolerable in most patients only using perithyroidal lidocaine injection. Moreover, apart from the usual problems of general anesthesia, monitoring of voice changes by nerve damage during the RFA procedure is impossible under general anesthesia. If voice change is detected during ablation, immediate cessation of RFA and injection of cold dextrose 5% in water (D5W) may recover voice problems induced

by thermal damage. Therefore, local anesthesia is a safer pain control method than general anesthesia. Although a large population multicenter study reported only 1% of voice-related complications during RFA of benign nodules,<sup>4</sup> a recent large population single-center study reported a higher incidence of nerve injury (including recurrent laryngeal nerve, spinal accessory nerve, and sympathetic ganglion) during treatment of recurrent thyroid cancers.<sup>5</sup> Therefore, current RFA guidelines recommend local anesthesia.

The authors stressed single-session RFA for benign TNs because they achieved acceptable results at 8-month follow-up. In addition, single-session RFA is cost-effective compared with the surgical procedure. However, we should consider the long-term results of thermal ablations (ie, radiofrequency or laser) for benign TNs. In long-term studies with single-session laser ablation (LA), there has been a tendency of marginal regrowth at 2- to 3-year follow-up. Døssing et al<sup>6</sup> reported that 35% patients (27 of 78 patients) had thyroid surgery because of an unsatisfactory result 67 months later following LA, mainly due to regrowth of the nodule. Valcavi et al<sup>7</sup> reported 9% (11 of 122 patients) recurrence rate at 3-year follow-up. Their volume reduction was maximum at 2 years but slightly decreased at 3 years. It is induced by regrowth of treated nodules. This phenomenon is commonly observed after single-session treatment by LA because tumor regrowth occurs gradually during a follow-up period after an initial improvement of the clinical symptoms. In the single-session study in Mayo Clinic, the authors reported a similar result. In Figure 2, volume reduction at 12 to 24 months was 54.3% but decreased to 52.8% at 24-month follow-up. This result suggests that marginal regrowth started during 12- to 24-month follow-up. In response to this phenomenon, Korean