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A historical viewpoint:
“The Gout of the Medici”

International Symposium on:
URIC ACID, GOUT AND BEYOND:
IS CV RISK A NEW OBJECTIVE?
Bologna (Italy), October 25th - 27th, 2012
The Medici were one of the most powerful families of the Italian Renaissance. Starting from the 14th century, their careful management of banking ventures and skilful political actions brought them to the forefront of social and political power in Tuscany and in Florence, the intellectual center of the Western world.

Lovers of art and science, the Medici were patrons of Michelangelo, Leonardo da Vinci, Botticelli, Galileo, and Benvenuto Cellini.
The ‘Medici Project’ is a multidisciplinary archaeological and palaeopathological investigation to perform the study of 49 funerary depositions of the Medici Grand Dukes, in the famous Medici Chapels of the Basilica of San Lorenzo in Florence. The Medici Project represents an unique opportunity to reconstruct the health and lifestyle of the members of this important family of the Italian Renaissance. Up until now 15 tombs, including the burials of nine children, have been investigated.

The crypt of the Basilica of San Lorenzo in Florence, Mausoleum of the Grand Dukes of the Medici Family.
Gout in pre-modern Medicine

The word gout was first introduced in the 13th century and derives from the Latin gutta, which means “drop”, similar to a liquid falling on the foot. This term reflects the theory according to which this condition was caused by an imbalance of a humour entering the affected joint, causing pain and inflammation.

It should be remembered that the term “gout” was used in those times to indicate several, different pathological conditions of rheumatic origin.

The distinction between gout and rheumatism was introduced later in the 17th century.
The clinical history of the Medici family is well known from the rich archives that were examined and published in the fundamental work of the Florentine physician and historian Gaetano Pieraccini.

Gaetano Pieraccini
(1864-1957)
From these records it emerges that several members of the Medici family suffered from arthritic diseases *

The term frequently reported by contemporary sources to indicate these morbid episodes, characterized by violent pain in the hands, feet, shoulders, knees and thoracic-lumbar spine, is ‘gout’.

Gout, also called the ‘disease of kings’ for its association with a lifestyle typical of the upper classes, seems to have been a family disease among the Medici, as attested by the nickname “the Gouty” attributed to Piero (1416–1469).

“Gout” is reported in the clinical history of Piero the Gouty (1416–1469), Cosimo I (1519-1574), Ferdinand I (1549-1609), Cardinal Carlo (1596-1666), Lorenzo (1599-1648), Cosimo II (1590-1621), Cardinal Giovanni Carlo (1611-1663), Prince Matthias (1613-1667), Cardinals Leopoldo (1617-1675) and Francesco Maria (1660-1711).
Palaeopathology allows to verify the nosological information obtained from the written sources and to clarify the nature of the rheumatological condition that afflicted the Medici.

Among the individuals studied so far, the skeletons of Cosimo “the Elder” (1389-1464), Piero “the Gouty” (1416–1469), Cosimo I (1519-1574), 1st Grand Duke of Tuscany, his son Ferdinand I (1549-1609), 3rd Grand Duke of Tuscany, and Cardinal Carlo (1596-1666) have shown evidence of arthritic diseases.
The “gout” of Cosimo I

The archive data indicate that Cosimo I suffered from several illnesses, including an acute articular disorder of the right knee, named ‘gout’ by the court physicians, which appeared at the age of 49 and 52–53 yrs.

The palaeopathological study of Cosimo’s remains reveals a series of articular lesions of the axial and appendicular skeleton. The skull shows hyperostosis *frontalis interna.*
The anterior longitudinal ligament on the right-hand side of the column is ossified at the level of the T6, T7 and T8 vertebral bodies; this flowing ossification forms a bony bridge between the vertebrae, appearing as a continuous line of bumps. Two other vertebrae, L2 and L3, are fused on the left-hand side through a bony bridge. Several thoracic and lumbar vertebrae present syndesmophytes, but without vertebral fusion. Marked bone spurs at the insertion of the ligamenta flava are also visible. Intervertebral disks and articular surfaces are normal.

The DISH of Cosimo I: lateral view of column with ossification of the anterior right vertebral ligament (arrows).
Ligament and tendon attachments of the appendicular skeleton show enthesopathies, in particular at the level of clavicles, *humeri, ulnae, radii*, coxal bones, femurs, *patellae, tibiae* and *calcanei*.

A diffuse arthritis affecting the lower thoracic and lumbar spine and the great joints is also visible.

The gout and DISH of Ferdinando I

As far as Ferdinand I is concerned, the historic documentation attests that he suffered from many acute attacks of gout, generally of the left foot, typically positioned in the big toe, from the age of 33 yrs until death.

The first attack seems to have been dated back to 1582, when Ferdinand wrote to his brother, the Grand Duke Francesco I, referring that he was confined to bed or chair because ‘…some catarrh has fallen down to my left foot. By God’s grace, may it not be podagra (i.e.: gout)!’. 
In 1591 the court physician Giulio Angeli accurately describes a typical gout attack:

‘yesterday the gout started to pinch the big toe of the Grand Duke’s left foot and then continued to advance rapidly! Overnight the toe has become swollen, inflamed and painful’.

The crises afflicted the Grand Duke also in the following years; furthermore, he started to become obese at the age of 41.
The skeleton of Ferdinand shows a peculiar lesion in the left foot.

The interphalangeal joint of the big toe presents cavitations, erosions and osteophytic margins.

At the peri-articular and articular surface of the joint a ‘scooped-out’ defect, with partial destruction of the subchondral plate, is also visible.

X-ray examination reveals an evident sclerotic margin, which involves both bones of the joint.

The gout of Ferdinand I: foot with lesion at the level of the interphalangeal joint of the hallux (arrow).
The paleopathological investigation carried out on the skeleton of Ferdinand I also reveals other pathological features similar to those observed in his father Cosimo. The vertebral bodies from T5 to T11 are fused in a unique block for the ossification of the right anterior ligament, conferring the typical aspect of a ‘candle wax’ to this spine segment.

The body of several cervical and thoracic vertebrae presents partial ossification of the right anterior ligament, but with no formation of bony bridges between the vertebrae. The intervertebral spaces and the apophyseal joints are normal. Ossifications of ligamenta flava, interspinal and supraspinal ligament insertions are largely present.

The DISH of Ferdinand I: the column with ossification of the anterior right vertebral ligament, at the level of the 5th–11th thoracic vertebrae bodies (arrows).

X-ray Prof. N. Villari
(University of Florence)
The extra-spinal ligaments show massive hyperostotic changes. Enthesopathies were present at the muscular insertion of clavicles, *scapulae, humeri, ulnae*, coxal bones, femurs, *patellae, tibiae* and *calcanei*. The thyroid cartilage and the epiglottis are ossified and well preserved. Large rough bilateral calcifications of the sternocostal cartilages of the first and of the last ribs are present, leading to a sternum with multiple ribs attached. Ferdinand I was affected by diffuse osteoarthritis, involving not only the spine and major joints, but also several articulations of his hands and feet.
The changes observed in Cosimo I and Ferdinand I meet the standard major criteria established for the diagnosis of diffuse idiopathic skeletal hyperostosis (DISH).

Both skeletons showed hyperostosis of the column, with the involvement of at least three contiguous *vertebrae* in Cosimo I, and up to seven *vertebrae* in Ferdinand.

Such changes were limited to the right side of the thoracic segment and diffuse ossifications of the articular ligaments and entheses were present.

Features often associated with DISH, such as hyperostosis *frontalis interna*, ossification of the neck and rib cartilages and massive osteoarthritis, confirm the diagnosis.

Among the five individuals belonging to the Medici family of >40 yrs of age that have been studied so far, two were affected by DISH.

Despite the narrowness of the sample, the high incidence of DISH in the Medici family is remarkable and a significant lifestyle indicator, supporting the link between social status and risk of developing DISH in mature age.

Botticelli (1470-75), Florence, The Adoration of The Magi
Paleopathological literature has reported several cases of DISH from different geographical sites and different periods; extensive studies have also been carried out to evaluate the incidence of DISH in large skeletal series.

The aetiology of this condition remains uncertain, but has been related to various metabolic disorders, in particular obesity and type II diabetes mellitus. Recent studies have highlighted a link between the incidence of diffuse idiopathic skeletal hyperostosis and high social status, with particular regard to lifestyle and nutritional patterns.

The Italian Renaissance aristocratic classes had access to a wide variety of food resources. Historical data report a diet based on wine and meat, occasionally enriched by eggs and cheese and, on penitential occasions, by fish. The consumption of vegetables was scarce and fruit was almost totally absent from alimentation.
A palaeonutritional study*, performed recently on the Medici Grand Dukes and their families, confirmed the written sources.

Carbon and nitrogen stable isotope analysis revealed a diet very rich in meat, as demonstrated by the $\delta^{15}N$ high values at the level of the carnivores.

The $\delta^{13}C$ values, related to fish consumption, revealed an intake of marine proteins at 14-30%.

The present study seems to further confirm the association between DISH and elite status.

High values of $\delta^{15}N$ in Ferdinand demonstrate a diet very rich in meat from terrestrial animals. $\delta^{13}C$ values show a minor integration with foods of marine origin (fish). This isotopic profile well correlates with the frequent attacks of gout referred by court chroniclers and with the diagnosis of chronic gout of the left big toe revealed by the paleopathological study.
The case of Ferdinand I is of particular interest for the diagnosis of gout, of which very little evidence has been found in paleopathology.

The typical skeletal and radiological features observed in the bone remains of Ferdinand I confirm the data reported by the written sources regarding the arthritic left foot gout which affected the Grand Duke.

Genetic and/or environmental factors, with particular regard to diet, may be involved in the aetiology of gout.

An alimentation rich in animal proteins, as attested by our paleonutritional investigation, may have favoured the onset of this disease.
Modern clinical studies report a significant association between DISH and gout.

Not only do the typical skeletal and radiological features observed in the bone remains of Ferdinand I confirm the data reported by the written sources regarding the left foot gout that affected the Grand Duke, but this represents the first documentation of the coexistence between diffuse idiopathic skeletal hyperostosis (DISH) and gout attested in palaeopathological literature.
The dorsal spine of Cosimo the Elder shows ossification of the anterior longitudinal ligaments on the right side, at the level of the last six vertebrae.

These features allow a clear diagnosis of Diffuse Idiopathic Skeletal Hyperostosis (DISH), which we also diagnosed in his descendants the Grand Dukes Cosimo I and Ferdinand I.

(data from Costa & Weber, 1955)
We know that from the age of 24 Cardinal Carlo suffered from an acute articular disorder of the feet, hands and knees, diagnosed as 'gout' by the physicians.

The documents report on 18 severe attacks from the ages of 35 to 59, with worsening between 60 and 65.

“The portraits”

The portraits, at about 60 years of age, show symmetrical severe arthropathy of the hands, with evident deformity and atrophy of the 1st, 4th and 5th fingers of the left hand.

Sustermans (c.1650), Florence, Palatina Gallery
The post-cranial skeleton shows an ankylosing disease, symmetrical and extremely severe, of the great and small articulations, characterized by:

- Fusion of the elbow (in flexion at 55°) (a, a’);
• Bilateral fusion of wrists, carpal bones, and some fingers (b, b’), with bilateral swan-neck deformity (c).
• Fusion of the right sacroiliac joint (d) (red arrow)

• Fusion of knees and *rotulae* (in flexion at 90°) (e)

X-ray Prof. N. Villari (University of Florence)
This data, together with the very severe osteoporosis, in particular of the lower limbs, demonstrates the cardinal’s total disability, in the last years of his life, as reported by the archival documents. Indeed, from 1658 (at the age of 63), the cardinal was no longer able to sign any letters or documents. In a letter to a nephew he writes: “Y(our) H(ighness) please excuse me for not being able to sign in my own hand (writing), because my hand does not work”

(4 December 1658)
The genotype of Cardinal Carlo de' Medici for the DRB1 and C loci was \textbf{DRB1*04/*11} and \textbf{(Cw*04/*12)*}.

Therefore, he was bearing the specificity \textbf{HLA-DR4} predisposing to \textbf{Rheumatoid Arthritis (RA)}.

The DRB1*11, Cw*04 (Cw4 in serology) and Cw*12 alleles are not involved in the onset of RA, PsA or other rheumatic diseases.

Piero “the Gouty” (1416-1469)

The post-cranial skeleton of Piero “the Gouty” shows an analogous picture of Rheumatoid arthritis*. There is an ankylosing disease, symmetrical and extremely severe, of the great and small articulations, characterized by:
- Fusion of wrists, carpal bones, and some fingers;
- Bilateral fusion of knees and *rotulae* (with legs fixed in hemi-flexion);
- Bilateral fusion of ankles, tarsal and metatarsal bones.

The intervertebral spaces are normal.

On the basis of the paleopathological study, the “gout” of the Medici is truly a uratic gout (associated with DISH) only in Ferdinand I, whereas it is Rheumatoid arthritis in Cardinal Carlo and Piero “the Gouty” and DISH in Cosimo the Elder and Cosimo I.

The nature of acute arthropathy of Prince Lorenzo, Cosimo II, Cardinal Giovanni Carlo, Prince Matthias and Cardinals Leopoldo and Francesco Maria, remains unclear.
In conclusion, the so-called “Medici Gout” has to be considered the clinical manifestation of three different and very common articular diseases, sometimes associated:

1. Diffuse Idiopatic Skeletal Hyperostosis (DISH)

2. Rheumatoid Arthritis (RA)

3. Gout

For this reason it is impossible to accept the proposal of a new historico-clinical entity, “the Medici Syndrome”, as recently suggested by some Authors*. 