

Assessment of Vitiligo Treatment Outcome: Review of Useful Methods

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Abstract: Many therapeutic modalities are available for vitiligo treatment. However, there is a lack of consensus about methods that assess the treatment outcome of the disorder. Comparative studies of various treatments of vitiligo, relied until recently on subjective methods based on an approximate evaluation of the extent of depigmented areas. Recently objective modalities that could be used to assess the changes in vitiligo lesions during treatment were described. Assessment could be based either on the global evaluation of vitiligo extent or on the changes of specific localized areas. Vitiligo Area Scoring Index, Vitiligo European Task Force evaluating method, Vitiligo Extent Tensity Index and Self Assessed Vitiligo Area Scoring Index are among the proposed methods for global assessment of vitiligo areas changes. Point counting methods, planimetry and digitizing methods are potentially useful methods for vitiligo outcome evaluation. However these methods are more suitable for measurement of localized vitiligo lesions and not for evaluation of vitiligo extent. Some simple methods used by physiotherapists in assessment of skin wounds, that could be applied to vitiligo will also be reviewed.

Keywords: Vitiligo, Objective Method, Computer Assisted, Assessment, Treatment

1. Introduction

Vitiligo is a serious cosmetic condition, mainly for individuals with dark skin. Since no particular therapy demonstrated its absolute superiority over others, various treatments are currently used to improve this skin disease. Comparison of various therapies used in vitiligo is necessary to guide the choice of physicians in the management of the disease. Usually vitiligo requires a long course treatment. Thus, the most effective and safe therapy and the less expensive should be selected to avoid side effects to the patients and to reach a low cost therapy. Since only a limited number of treated patients demonstrate complete repigmentation, treatment efficacy could not be easily evaluated by percentage of patients with complete repigmentation, but rather by assessment of changes occurring in the vitiligo lesions. How to evaluate these changes? No consensus exists about assessment of vitiligo. Should one consider the extension of vitiligo or size variation

of a particular treated lesion? Various methods assessing therapy efficiency have been used. However, vitiligo treatment outcome was usually assessed by subjective methods, while in other skin conditions like wounds and leg ulcers, variation in size of treated areas was evaluated by sophisticated methods of areas measurements. Only recently, some authors tried to develop new objective evaluating methods applied to vitiligo. The first attempts to evaluate vitiligo response to treatment will be reviewed, as well as the most recently used objective methods. Methods used to assess skin ulcers, that could be potentially used in the evaluation of vitiligo lesions will be discussed.

2. First Evaluative Methods for Global Assessment

2.1. Historical Aspects

Van Geel *et al.* [1] reviewed the literature that evaluated

the vitiligo surgical treatment outcome, and published between 1966 and 2003. They found that many of these evaluation methods rely on the subjective assessment of repigmentation by the investigator. In 14 studies (33%) repigmentation was recorded as an exact percentage. Ten studies (23%) used this parameter in a less strict sense, varying from 'more than 75% repigmentation' to 'less than 30%, 31-50, 51-75, 76-90 and 91-100%'. Four other studies (9%) qualified repigmentation as 'zero', 'partial' or 'complete' and 3 (7%) mentioned the presence of 'poor', 'moderate', 'fair', 'good' or 'excellent' results.

Some authors [2] classified repigmentation degree as follows: 0% to 25% repigmentation, poor; 26% to 50%, moderate; 51% to 75%, good, and 76% to 100%, excellent. Because of its simplicity, this method was extensively used in the literature, but, could not be considered enough accurate to allow valid comparative studies.

2.2. Objective Methods for the Assessment of Vitiligo Extent

Currently, simple but not enough accurate methods to assess the involved body surface area are used: 'the rule of nine' and the flat hand method.

2.2.1. The "Rule of Nine" Method

The rule of nine' assumes that the total body surface area comprises 9% for head/neck, each arm, leg and the four trunk quadrants, leaving 1% for the genitalia.

2.2.2. The Flat Hand Method

In the 'flat hand = 1%' method, a flat hand represents 1% of the total body surface area.

However, both methods are based on visual assessment and require some degree of subjective intervention by investigators.

3. Recent Objective Methods for Global Assessment

3.1. Vitiligo Area Scoring Index (VASI)

More recently, clinicians expressed the need for objective methods that assess extension of achromic lesions. This is to allow follow up of treatment efficacy in patients, or to compare controlled studies. The Vitiligo Area Scoring Index (VASI) was developed analogous to the PASI (Psoriasis Area and Severity Index) score used in psoriasis evaluation. VASI is a standardised, sensitive method and easy to perform, although the investigator intervention could be considered partly subjective. [3] The body of the patient is divided into five separate regions: hands, upper extremities (excluding hands), trunk, lower extremities (excluding the feet), and feet. The axillary and inguinal regions are included with the upper and lower extremities, respectively. Depigmentation within each area is estimated to the nearest of one of the following percentages: 0, 10, 25, 50, 75, 90, or 100%. For each body region, the VASI was determined by the product of the area of vitiligo in hand units (which was set at 1% per

unit) and the extent of depigmentation within each hand unit-measured patch (possible values of 0, 10%, 25%, 50%, 75%, 90%, or 100%). These 2 steps of evaluation by the investigator partly include a subjective note. The total body VASI was then calculated using the following formula by considering the contributions of all body regions (possible range, 0-100):

$$\text{VASI} = \sum_{\text{All Body Sites}} \text{Hand Units} \times \text{Residual Depigmentation. [3]}$$
 The advantage of VASI score method is that it gives a global assessment of all lesions.

3.2. Vitiligo European Task Force (VETF) Evaluating Method

Due to lack of consensus in methods of assessment of vitiligo, which makes impossible to compare the outcomes of different studies of the same treatment, VETF proposed a consensus for assessment of vitiligo treatment outcomes using a system which combines analysis of extent, stage of disease (staging), and disease progression (spreading). [4] Extent is evaluated using the rule of 9. Staging (severity) is based on cutaneous and hair pigmentation in vitiligo patches, and the disease is staged 0–3 on the largest macule in each body region, except hands and feet, which are assessed separately and globally as one unique area. Assessment of spreading (progression of disease) is based on Wood's lamp examination of the same largest macule in each body area. Wood's lamp is useful for a combined assessment of staging and spreading in the same selected area. The authors suggested that depigmentation scale of VASI and VETF extent scale could be combined in future studies and, for studies evaluating treatments, a combination of the VETF scale and an objective assessment of some target lesions by computer analysis of digital images could be more suitable than VETF evaluating method.

3.3. Vitiligo Extent Tensity Index (VETI) Score [5]

The VETI score combines analysis of extensity and severity of vitiligo. The rule of nines is used to evaluate the percentage of extension involvement. Disease severity is scored by using five stages of disease tensity. Five sites, head, upper limbs, trunk and lower limbs and genitalia are separately scored:

Stage 0: Normal skin

Stage 1: Hypopigmentation

Stage 2: Complete depigmentation with black hair and with perifollicular pigmentation

Stage 3: Complete depigmentation with black hair and without perifollicular pigmentation

Stage 4: Complete depigmentation with compound of white and black hair with/without perifollicular pigmentation

Stage 5: Complete depigmentation plus significant hair whitening

The total body VETI is calculated using the following formula:

VETI score: (Percentage of head involvement \times grade of tensity) + (Percentage of trunk involvement \times grade of

tensity) 4+ (Percentage of upper limbs involvement \times grade of tensity) 2+ (Percentage of lower limbs involvement \times grade of tensity) 4+ (Percentage of genitalia involvement \times grade of tensity) 0.1

The coefficients reported in this formula are based on percent of skin surface by the rule of nines.

4. Subjective Method for Global Assessment

4.1. Self Assessed Vitiligo Area Scoring Index (SAVASI) [6]

In an attempt to make the patient involved in the management of the disease and to improve communication between patients and physicians, the authors developed the SAVASI based on the VASI. SAVASI is a patient-oriented measurement tool for vitiligo, that allows patients to assess the degree of depigmentation of their vitiligo. Firstly the patient indicates in a drawing the body parts affected by vitiligo. Thereafter, the patient assesses per body part the number of hand units affected (a patient's own hand set at 1% of the body surface area per unit) and the extent of depigmentation within these affected hand units (possible values of 0, 10, 25, 50, 75, 90 or 100%.

The correlation between the SAVASI and VASI was high.

47% of patients assessed the questionnaire as very easy or easy, 45% not easy-not hard and 8% assessed the questionnaire as hard. None of the patients assessed the questionnaire as very hard.

5. Objective Methods to Assess Localized Vitiligo Lesions

More objective methods, with less intervention degree from the investigator, are the point counting method, planimetry and digitizing methods. These methods give objective measurement, but are more commonly applied to measure a specific and localized area and could not be used to assess the total extension of vitiligo lesions:

5.1. Point Counting Method

The point counting method is a simple, practical, and an accurate technique, which is used to estimate the irregularly shaped sectional surface area. [7] The borders of the lesions are marked with an ordinary ballpoint pen and a piece of paper is placed over the lesion as for each lesion, the copied borders of projection areas are enhanced by redrawing the contours with a pen. In order to estimate the number of points, a transparent sheet that has points (+) printed on it is randomly superimposed on lesion projection area (Figure 1). The numbers of intersections hitting the area of interest are counted. The total area of each lesion is estimated by multiplying the representative area of a point on grid by total number of points counted for the lesion.

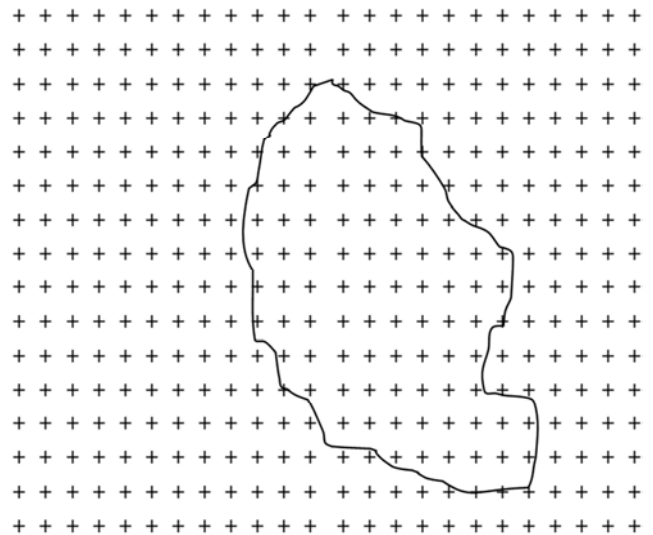


Figure 1. Point counting method: a transparent sheet filled with equidistant marks (+) is randomly superimposed to the outlined borders of the lesion.

5.2. Planimetry [7]

A planimeter is a measuring instrument used to determine the area of an arbitrary two-dimensional irregular shape, based on the Green's theorem. There are several kinds of planimeters, but all operate in a similar way. Planimeters have been in use for some time and are adapted for ascertaining the areas of irregular figures. The planimeter comprises an elongated arm provided at one end with a fixed point and at the other end with a tracing point. The operator moves the tracing point of the planimeter along the curve. The length of the curve is proportional to the area delineated by the curve. Modern planimeters use Green's theorem which relates the double integral over a closed region to a line integral over its boundary to calculate the area bounded by a closed curve.

5.3. Digitizing Methods

Digitizers were popularized in the mid 1970s and early 1980s. Various tools used digitizing methods, including digitizing tablets, computer-aided design (CAD) software and 2-D Computerized image analysis.

5.3.1. Graphics Tablets

A graphics tablet (also called pen pad or digitizer or digitizing tablet) consists of a flat surface upon which the user may draw an irregular figure using an attached stylus. The image generally does not appear on the tablet but, rather, is displayed on the computer monitor. Capturing data in this way, either by tracing or entering the corners of linear polylines or shapes is called digitizing. A metric scale could be positioned on the adjacent skin for calibration and results are then expressed in metric units (i.e. cm²).

New developments have been also introduced to improve digitizing methods: a new digital image analysis system has been used for 2 D surface assessment of vitiligo lesions and compared to a 3 D measurement. By this photographic method, the user indicates a spot which belongs to the

vitiligo lesion. Then the image analysis algorithm tries to expand the region by including neighbouring pixels if they are similar to the colour of the indicated spot, based on uniform colour space called CIE $L^*a^*b^*$. [8]

For the 3D measurement, lesions were copied onto transparent sheets by putting the sheet over the lesion and tracing the lesion contours. This has the advantage of taking the local curvature into account, thereby avoiding possible underestimation of the lesion surface due to the move from 3 to 2 dimensions. In both methods, once the whole lesion is selected, the area is analyzed using simple image processing techniques implemented in Malabo (The MathWorks, inc). The estimated reproducibility of this method (scanning, segmentation and measurement) for a plane surface is in the order of 98% or more. (CV or coefficient of variation is 2%). Sparing time was an advantage of the 2D method over the 3D method.

Comparing the 2D with the 3D measurements, a systematic underestimation was demonstrated, even for the relatively 'flat' and small lesions. This is an important restriction of the system.

The authors concluded that the method is not good enough for absolute surface measurements of large areas, but rather for the estimation of surface changes over time of some selected target lesions. [8] However, we think that even when comparing the area variation over time of the same lesion, some changes of curvature may occur as the lesion get smaller, a bias that could have an impact in the 2D method and not in the 3D method.

5.3.2. CAD (Computer-Aided Design) Method

CAD (computer-aided design) software is used by architects, engineers, drafters, artists, and others to create precision drawings or technical illustrations. CAD software can be used to create two-dimensional (2-D) drawings or three-dimensional (3-D) models.

AutoCAD 2000 (Autodesk®, USA) allows also calculation of areas of irregularly shaped vitiligo lesions. [9] A transparent sheet is placed over the vitiligo lesion and the border outlined with an ordinary pen. The user traces the edge profile of vitiligo lesions on the screen either by retracing the scanned image or outlining the figure of the transparent sheet applied to the screen using the mouse.

In case of scanned image, the consecutive following steps are needed to display the figure on the screen: *insert* → *raster image*. Then the user should select the image file, *show preview* → *open* → *OK* → *enter*. The next step is to draw the border of the lesion either by using the scanned image or the sheet applied to the screen: *draw* → *polyline*. The first click on the border of the figure initiates the drawing. Subsequent movements of the mouse by clicking away from the previous location outline the border of the lesion. The last point will be connected to the first point by clicking on the enter button of the key board. In case of scanned figure, the user retraces the edge of the figure displayed on the screen, using the mouse. In case of the figure applied to the screen, a blank page of the software is opened and the user traces the edge

profile of the figure using the mouse following the border of the image applied to the screen. Once the border is outlined, the next steps are followed to obtain area measurement: click on *tools* → *inquiry* → *area*. Then tape "O" for "object" in the bottom of the screen in front of "*specify first corner or [Object/Add/Subtract]*" → *enter*. Then click with the mouse on a randomly chosen point of the outlined border to display the lesion dimensions (area and perimeter) (Figure 2).

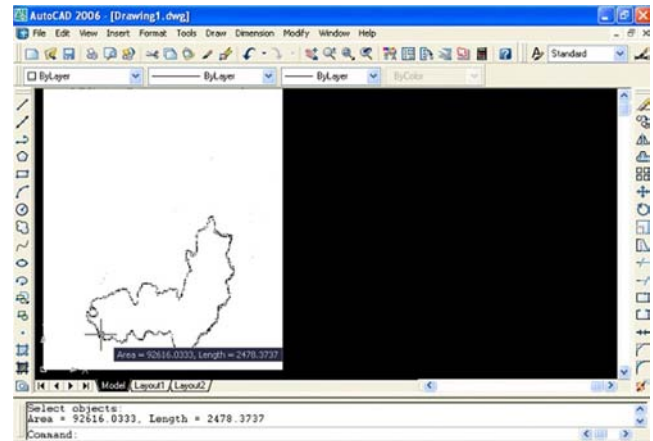


Figure 2. CAD (computer-aided design) method: software displays calculated area and perimeter.

5.3.3. 2-D Computerized Image Analysis [10]

To evaluate the efficacy of cultured melanocyte transplantation versus non-cultured epidermal cell transplantation on stable vitiligo, three-dimensional analysis (using graph paper) and 2-D computerized analysis (using measuring tool of Adobe Acrobat XI software, Adobe System) showed similar results. To evaluate the percent area repigmented using photographs, they were converted to PDF format and the measuring tool of the Adobe acrobat reader XI software was used to trace the outline of the lesion. The measuring tool determined the area covered by the outlines. Once the respective areas were drawn, the software displayed the respective measured areas.

6. Wounds Evaluative Methods

Objective methods have been used for decades by physiotherapists to assess wound areas in order to compare therapeutic modalities in controlled studies. These methods although not used in vitiligo, could be considered for this purpose.

6.1. Metric Graph Paper Method

A method that entailed tracing ulcers on transparent paper, placing the tracing over metric graph paper, and counting the number of square centimeters within the tracing is used to measure wound area. [11] The counting procedure entailed tracing the outline of the tracing on metric graph paper and counting the number of square millimeters within the tracing.

Counting the number of square millimeters within a tracing, however, can be a tedious task that can take minutes

for each tracing. Furthermore, cutting the tracing from the film to transfer the outline to the graph paper may affect the accuracy of the method.

6.2. Weighing Method

The weighing procedure involves weighing the tracings on balance. [11] Tracing's mass is divided by the previously determined mean mass of the film per square centimeter to yield a calculated area for each tracing.

The weighing method similarly involves cutting the tracing from the film and requires access to a precise scale, the cost of which may be prohibitive.

7. Comparative Studies

Planimetry, digitizing techniques, point counting method, metric graph paper and weighing methods have been compared in different experimental studies, either in vitiligo or area wound measurements. Accuracy, as well as financial and practical aspects have been evaluated.

7.1. Planimetry/Vs Digitizing Technics

In a comparative study between planimetry and digitizing technics, the authors applied these 2 methods for wound area measurement. [12] A Planix 7 digital planimeter and a digitizing table were used to calculate areas. Digitizing table was used to trace the wound outline. Software for calculation of wound area was specifically developed for this purpose.

The digitizing (compared with planimetry) was identified as the more reliable measurement method. However, lack of availability of the digitizing software for practitioners, comparatively to commercially available planimeters, could restrict the use of this method.

7.2. Point-Counting Method /Vs Digital Planimetry

Point-counting method and digital planimetry method were compared to assess area of vitiligo lesions. [7] For digital planimetry, a calibration square with 1 cm² area was used, in order to convert the area from pixel to cm². Areas measured by planimetry and point counting method have been shown to be statistically similar. However the cost and amount of equipment and time required to use computer assisted planimetry restricts its clinical usefulness in daily practice.

These two methods have also been compared in wound area measurement. The authors concluded that since precision of computer-aided planimetry is comparable to point counting method, but this latter being so simple and cheap, it is ideally suited for the daily work of accurately recording the sizes of lesions. [13]

7.3. Metric graph Paper/Vs Planimetry/Vs Digitizing Technic

These 3 methods have been compared by measuring wound surface area from transparency film tracings. [14]

Wound area measurements were obtained in 31 subjects with venous stasis ulcers. After tracing each wound on

transparency film, wound area was calculated by placing the transparency film over graph paper and counting the squares, using a planimeter, and using a digitizer. Results of this study indicate that wound measurements can be taken reliably with the graph paper, planimeter, and digitizer methods. The graph paper technique may be preferable in most clinical settings, because it is low in cost and easy to use.

These methods could be considered for use in assessment of vitiligo specific lesions.

7.4. Sonic Digitizer/Vs Digitizing Tablet/Vs Weighing Method

A direct sonic digitizing method was developed for wound area measurement and compared to weighing and digitizing tablet methods. [15]

None of these two last techniques gives an immediate indication of ulcer size. A sonic digitizer, a device that makes direct measurements was used. The digitizer has a stylus with an ultrasonic pulse generator. The pulse is initiated by a hand-held microswitch and picked up by two point microphones. Internal timing circuits enable the position of the stylus to be estimated to an accuracy of 0.1 mm. The Cartesian co-ordinates of the digitized point were then sent to a microcomputer to display the traced shape on the screen, and to calculate the area and circumference of the traced object. The correlation coefficient between the weighing technique and the sonic digitizer was 0.98, and between the digitizing tablet method and the sonic digitizer it was 0.99. In each case the slope of the regression line was very close to 1. There was no difference in the time required to trace the ulcers with the sonic digitizer or using a plastic sheet. However, the area or circumference was immediately available from the sonic digitizer, but further time-consuming cutting or tracing was necessary to find the area by either of the other two techniques. These results confirm the accuracy of the sonic digitizer as a rapid and useful method of measuring venous ulcers. This method could be considered for vitiligo lesions area measurement.

8. Global Vitiligo Assessment / Vs Localized Area Measurement

Hamzavi *et al.*, [3] developed the Vitiligo Area Scoring Index (VASI) analogous to the Psoriasis Area Scoring Index (PASI). Globally, the limitation of the digitizing methods is that only a limited number of lesions can be studied for each patient, in contrast to the VASI or VETF methods that consider the extent of the lesions and their clinical aspect. However, evaluating the treatment outcome requires comparison of symmetrical and similar lesions. Knowing that the severity of vitiligo could be assimilated with resistance to treatment, extensive lesions do not necessarily undermine severity. Response to treatment depends largely on the lesions topography (the extremities are more difficult to treat than the face or the trunk, even though surface of these lesions are limited, and extensive truncal lesions could

respond more rapidly than limited lesions of the fingers, even in case of extensive lesions) and the degree of depigmentation. Thus, in our opinion, assessing the efficacy of a treatment needs comparison of limited, similar and symmetrical lesions by evaluating surface changes, rather than comparison of global areas which could be influenced by high topographic variabilities between patients.

9. Conclusion

Global assessment methods, either VASI, VETF or VETI are better indicated to evaluate treatment outcome in patients with time, although a limitative aspect of these methods could be the subjective intervention of the investigator. The more objective methods could be used in order to compare different treatment modalities, on the basis of left-right comparison studies to avoid inter serial variabilities. In addition, these objective methods could also be used to compare reported series in the literature. For this purpose, ideally, vitiligo measurements should be accurate (reflect the actual dimensions of the lesion), reproducible (different investigators should obtain the same measurement), sensitive (able to detect small changes), standardized (one that can be used as a basis for comparison, either from time to time for a single patient or among patients in different groups and one that lends itself to statistical analysis), Digitizing methods seem more suitable to fit these conditions. However, the prohibitive cost of the equipment could restrict the use of these objective methods. An alternative would be the point counting method.

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