RECOMMENDATIONS

- From the results of this study, it is recommended to periodically follow up chronic Hepatitis C patients with genotype 4 for glucose abnormalities and anticipate their occurrence.

- Implementation of new guidelines in Hepatitis C genotype 4 treatment, involving pretreatment screening for insulin resistance using HOMA-IR test, being an easy and practical one.

- Studies determining cut off value for HOMA-IR test as a definitive method for determining insulin resistance in Egyptian patients with genotype 4.

- Considering management of insulin resistance in patients who are candidates for treatment using dual therapy pegIFN/RBV, through lifestyle modification or even using antidiabetics as metformin.

- Large studies are needed to test the effect of insulin resistance on new treatment modalities using the newly approved DAA drugs as sofusbuvir and ledipasvir.

- Further studies are needed to establish the direct role of HCV in development of insulin resistance in chronic hepatitis C patients addressing multiple pathways.

- More studies are needed to follow up the treated patients who showed insulin resistance, for a longer period of time after stopping treatment to rule out rebound or increase in HOMA-IR.

- Larger studies with larger studied population are needed to confirm the metabolic role in development of insulin resistance in CHC patients.

- Follow up studies for the effect of insulin resistance on liver functions and fibrosis progression, are needed.

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الملخص العربى

يقدر عدد مرضى الإلتهاب الكبدي الفيروسي سي بحوالي 170 مليون نسمة، يمثلون حوالي 3٪ من سكان العالم. التهاب الكبد الفيروسي هو أهم مشكلة صحية عامة تواجه مصر اليوم. وتقدر معدلات انتشار فيروس (سي) في عموم السكان ما بين 10٪ و 15٪ في المناطق الريفية، مع بعض الفئات العمرية الذين يعانون من معدلات انتشار تصل إلى 50٪. ومنذ عام 2006 حققت مصر تقدما كبيرا في السيطرة على الإلتهاب الكبدى الفيروسي حيث أسست لجنة وطنية لمكافحة الإلتهاب الكبدي الفيروسي مكونة من 23 وحدة علاج إلتهاب الكبد الفيروسي موزعة على كافة أنحاء البلاد كجزء من برنامج الحملة القومية لعلاج هذا المرض و الذي أطلق في عام 2008. وبين عامي 2006 و 2012 تم علاج أكثر من 220000 مريض في مراكز العلاج القومية وعيادات التامين الصحى. و تتم حاليا معالجة المرضى المصريين المصابين بفيروس سي عن طريق تلقي 48 جرعة أسبوعية تحت الجلد من الإنترفيرون مع جرعة مرتين يوميا من عقار ريبافيرين، مع العلم أن مخططات العلاج الجديد بعقار سوفوسبوفير في طريقها للتنفيذ.

في عام 1994 و للمرة الأولى ذكرت تقارير لأليسون و آخرون انه يوجد علاقة بين مرض السكري النوع الثاني والإلتهب الكبدي المزمن ، حيث لاحظ أن انتشار مرض السكري النوع الثاني كان أعلى بكثير في حالات تليف الكبد المتعلقة بالإلتهاب الكبدي الفيروسي سي من تلك المصاحبة لتليف الكبد الناتج عن أمراض الكبد الأخرى. و لقد تمت دراسة الأدلة التي تظهر تأثير الإلتهاب الكبدي الفيروسي سي في تسبيب مرض السكري وكذلك تأثيره المناعي من خلال تحفيز استجابة الخلايا اللمفاوية TH1 و التي بدورها تعمل على تنشيط عامل (TNF) نظام -α وارتفاع مستويات انترلوكين 6. إن الأنسولين يؤثر بيولوجيا من خلال تحفيز مستقبلات الأنسولين 1 (IRS-1) و 2 (IRS-2). إن وجود مستويات عالية من TNF-α يكون أحد القواعد الأساسية لمقاومة الانسولين (IR)، والتي تعمل من خلال التأثير على التيروزين الداخل في تكوين مستقبلات الأنسولين (IRS -1)، وهو جزيء أساسي في تحفيز إفراز الأنسولين.

العلاقة بين الإلتهاب الكبدي الفيروسي سي و مقاومة الأنسولين لها عواقب سريرية كبيرة. أدلة متزايدة تشير إلى أن مقاومة الانسولين المصاحبة للإلتهاب الكبدي الفيروسي سي قد تسبب تسارع تليف الكبد، وانخفاض الاستجابة للعلاج بالإنترفيرون و سرعة الإصابة بسرطان الكبد. وترتبط زيادة مستويات مقاومة الأنسولين مع انخفاض معدلات الاستجابة الفيروسية الأولية للعلاج وكذلك الاستجابة الفيروسية المستمرة في مرضى الإلتهاب الكبدي المزمن الذين يعالجون بمزيج من الإنترفيرون وعقار ريبافيرين. وهذا يعني أن وجود حالات من مقاومة الأنسولين قبل الإصابة بمرض السكري يجب أن يتم تشخيصها حيث يعتبر تحليل (HOMA-IR) وسيلة سهلة لتشخيص مثل تلك الحالات.

لقد كان هدفنا تقييم مدى انتشار مقاومة الانسولين لدى المرضى المصرين المصابين بالنمط الجيني 4 لفيروس التهاب الكبد المزمن سي، وتقييم العوامل المرتبطة بمقاومة الأنسولين في هؤلاء المرضى واختبار تأثير مقاومة الانسولين على نتائج العلاج.

وكان معدل HOMA-IR بالمرضى 31% > 3.0، ومتوسط مؤشر كتلة الجسم للمائة مريض المصابين بإلتهاب الكبد المزمن و المدرجين بالدراسة كان 27.60 مع متوسط ± 27.06 SD ± 3.44، وكانت متلازمة التمثيل الغذائي موجودة في 15٪ منهم. أما بالنسبة للدراسة المناعية و الهيستوكيميائية لIRS-1 في 29 عينة للكبد مختارة من هؤلاء المرضى: 15 حالة أظهرت صبغة ضعيفة ل 10-50٪ أو أقل من خلايا الكبد وأظهرت 14 حالة صبغة قوية ل 50٪ أو أكثر من خلايا الكبد.

وأظهرت دراسة العلاقة بين مقاومة الانسولين ، العمر، مؤشر كتلة الجسم، كمية ال HCV-RNA قبل العلاج فى الدم ، معدلات الدهون، مرحلة التليف الكبدي و درجة دهون الكبد فروق ذات دلالة إحصائية بين HOMA-IR والمستوى الفيروسي المبدئي ومرحلة التليف الكبدي و ذلك عندما تم تحليل البيانات بواسطة الانحدار الخطي متعدد المتغيرات، وتشير النتائج إلى أن المستوى الفيروسي المبدئي بقي العامل المستقل الوحيد المرتبط بإرتفاع معدل HOMA-IR (p = 0.001). أما بالنسبة للتحليل أحادي المتغير من المتغيرات التي تؤثر على نتائج العلاج كشفت هذه الدراسة أن في سن أصغر، انخفاض درجات HOMA-IR ، وانخفاض مستوى خط الأساس RNA-HCV والدرجات القليلة من دهون الكبد، ارتبطت بشكل كبير مع الاستجابة للعلاج لدى المرضى المدرجين بهذه الدراسة. وأظهر التحليل متعدد المتغيرات اللوجستي أن المستوى الفيروسي الأساسي المنخفض بالدم بقي العامل المستقل الوحيد المرتبط بالاستجابة للعلاج.

وتبين هذه النتائج أن الإصابة بمرض إلتهاب الكبد المزمن بفيروس سي النمط الجيني 4 يكون مصحوب بإرتفاع معدل انتشار مقاومة الأنسولين. و يظهر أيضا أن المرضى الذين يعانون من مقاومة الأنسولين أكثر عرضة لفشل العلاج بألفا انترفيرون مع عقار ريبافيرين. و يظهر أيضا أن مقاومة الانسولين تتحسن مع العلاج الناجح.